



US009255125B2

(12) **United States Patent**
Reed

(10) **Patent No.:** US 9,255,125 B2
(45) **Date of Patent:** *Feb. 9, 2016

(54) **POLYNUCLEOTIDES ENCODING EXTRACELLULAR-SIGNAL-REGULATED KINASE (ERK) HETEROPOLYLIGAND POLYPEPTIDES**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 27 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/612,458**

(22) Filed: **Sep. 12, 2012**

(65) **Prior Publication Data**

US 2014/0099668 A1 Apr. 10, 2014

Related U.S. Application Data

(63) Continuation of application No. 11/983,235, filed on Nov. 8, 2007, now Pat. No. 8,283,445.

(60) Provisional application No. 60/865,589, filed on Nov. 13, 2006.

(51) **Int. Cl.**

C07K 14/00 (2006.01)
A61K 38/00 (2006.01)
A61K 38/16 (2006.01)
C12P 21/02 (2006.01)
C07K 14/47 (2006.01)
C12N 15/62 (2006.01)
C12N 15/85 (2006.01)

(52) **U.S. Cl.**

CPC *C07K 14/001* (2013.01); *C07K 14/47* (2013.01); *C12N 15/62* (2013.01); *C12N 15/85* (2013.01); *C07K 2319/21* (2013.01); *C07K 2319/43* (2013.01); *C07K 2319/60* (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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ABSTRACT

The invention relates to kinase inhibitor ligands and polyligands. In particular, the invention relates to ligands and polyligands that modulate ERK activity. The ligands and polyligands are utilized as research tools or as therapeutics. The invention includes linkage of the ligands and polyligands to a cellular localization signal, epitope tag and/or a reporter. The invention also includes polynucleotides encoding the ligands and polyligands.

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LIGAND X	LIGAND X
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FIGURE 1A

LIGAND X	LIGAND X	LIGAND X
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FIGURE 1B

LIGAND X				
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FIGURE 1C

LIGAND X	SPACER	LIGAND X
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FIGURE 2A

LIGAND X	SPACER	LIGAND X	SPACER	LIGAND X
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FIGURE 2B

LIGAND X	LIGAND X	SPACER	LIGAND X	SPACER	LIGAND X
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FIGURE 2C

LIGAND X	LIGAND Y
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FIGURE 3A

LIGAND X	LIGAND Y	LIGAND Z
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FIGURE 3B

LIGAND X	LIGAND Y	LIGAND X	LIGAND Z	LIGAND A
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FIGURE 3C

LIGAND A	LIGAND B	LIGAND C	LIGAND D
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FIGURE 3D

LIGAND A	LIGAND A	LIGAND B	LIGAND C
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FIGURE 3E

LIGAND B	SPACER	LIGAND A
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FIGURE 4A

LIGAND Z	SPACER	LIGAND Y	SPACER	LIGAND X
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FIGURE 4B

LIGAND X	SPACER	LIGAND B	SPACER	LIGAND C	SPACER	LIGAND D	SPACER	LIGAND E	SPACER	LIGAND F
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FIGURE 4C

LIGAND A	SPACER	LIGAND B	SPACER	LIGAND C	SPACER	LIGAND D	SPACER	LIGAND E	SPACER	LIGAND F
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FIGURE 4D

LIGAND X	SPACER	LIGAND Y	SPACER	LIGAND Z	SPACER	LIGAND A	SPACER	LIGAND B	SPACER	LIGAND C	SPACER	LIGAND D	SPACER	LIGAND E	SPACER	LIGAND F
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FIGURE 4E

LIGAND C	SPACER	LIGAND Y	SPACER	LIGAND Z	SPACER	LIGAND Y	SPACER	LIGAND C
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FIGURE 4F

LIGAND X	LIGAND X	EPITOPE
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FIGURE 5A

EPITOPE	LIGAND X	LIGAND Y
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FIGURE 5B

LIGAND X	SPACER	LIGAND X	EPITOPE
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FIGURE 5C

EPITOPE	LIGAND X	SPACER	LIGAND Y
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FIGURE 5D

LIGAND X	SPACER	LIGAND Y	SPACER	LIGAND A	LIGAND B	EPITOPE
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FIGURE 5E

EPITOPE	LIGAND X	SPACER	LIGAND Y	LIGAND A	LIGAND B
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FIGURE 5F

LIGAND X	EPITOPE
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FIGURE 5G

LIGAND X	LIGAND X	REPORTER
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FIGURE 6A

REPORTER	LIGAND X	LIGAND Y
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FIGURE 6B

LIGAND X	SPACER	LIGAND X	REPORTER
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FIGURE 6C

REPORTER	LIGAND X	SPACER	LIGAND Y
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FIGURE 6D

LIGAND X	SPACER	LIGAND Y	SPACER	LIGAND A	LIGAND B	REPORTER
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FIGURE 6E

REPORTER	LIGAND X	SPACER	LIGAND Y	LIGAND A	LIGAND B
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FIGURE 6F

LIGAND X	REPORTER
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FIGURE 6G

LIGAND X	LIGAND X	LOCALIZATION SIGNAL
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FIGURE 7A

LOCALIZATION SIGNAL	LIGAND X	LIGAND Y
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FIGURE 7B

LIGAND X	SPACER	LIGAND X	LOCALIZATION SIGNAL
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FIGURE 7C

LOCALIZATION SIGNAL	LIGAND X	SPACER	LIGAND Y
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FIGURE 7D

LIGAND X	SPACER	LIGAND Y	LIGAND B	LOCALIZATION SIGNAL
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FIGURE 7E

LOCALIZATION SIGNAL	LIGAND A	LIGAND B	LIGAND C	LIGAND D
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FIGURE 7F

LOCALIZATION SIGNAL	LIGAND Y
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FIGURE 7G

LIGAND A	LIGAND B	LIGAND C	LIGAND D	EPITOPE	LOCALIZATION SIGNAL
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FIGURE 8A

LOCALIZATION SIGNAL	LIGAND X	LIGAND Y	EPITOPE
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FIGURE 8B

EPITOPE	LIGAND X	SPACER	LIGAND X	LOCALIZATION SIGNAL
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FIGURE 8C

LOCALIZATION SIGNAL	LIGAND X	SPACER	LIGAND Y	EPITOPE
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FIGURE 8D

EPITOPE	LIGAND X	LIGAND Y	LIGAND B	LOCALIZATION SIGNAL
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FIGURE 8E

LOCALIZATION SIGNAL	LIGAND Z	SPACER	LIGAND Y	LIGAND B	EPITOPE
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FIGURE 8F

EPITOPE	LIGAND B	LOCALIZATION SIGNAL
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FIGURE 8G

PROMOTER	LIGAND or POLYLGAND	EPIPOPE	LOCALIZATION SIGNAL	STOP	POLY-A
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FIGURE 9A

PROMOTER	OPTIONAL REPORTER	OPTIONAL EPIPOPE	LIGAND or POLYLGAND	OPTIONAL LOCALIZATION SIGNAL	STOP	POLY-A
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FIGURE 9B

PROMOTER	LIGAND or POLYLGAND	REPORTER	LOCALIZATION SIGNAL	STOP	POLY-A
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FIGURE 9C

PROMOTER	LIGAND or POLYLGAND	OPTIONAL EPIPOPE	OPTIONAL REPORTER	OPTIONAL LOCALIZATION SIGNAL	STOP	POLY-A
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FIGURE 9D

PROMOTER	LIGAND or POLYLGAND	LOCALIZATION SIGNAL	STOP	POLY-A
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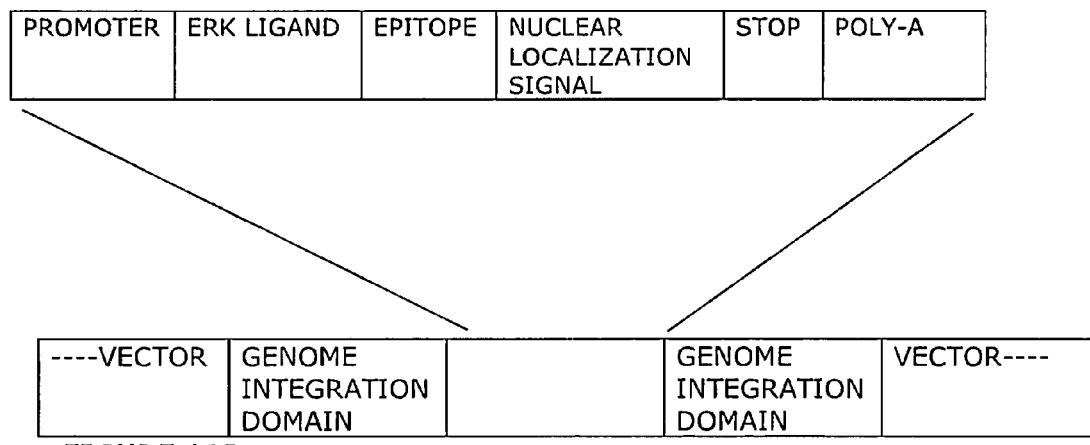
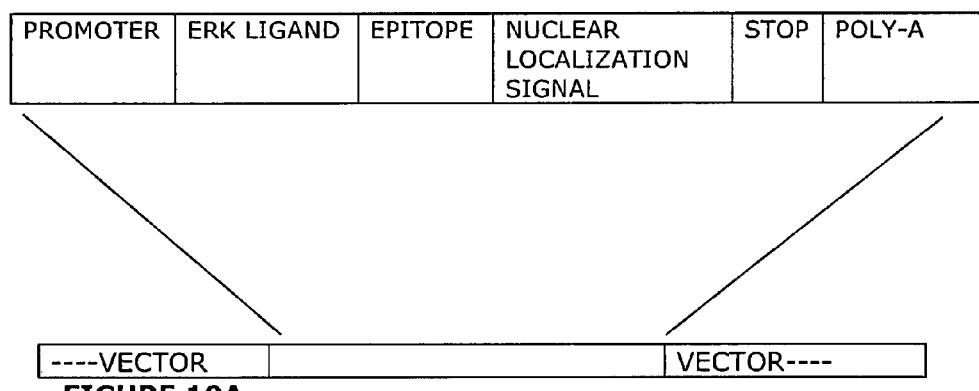
FIGURE 9E

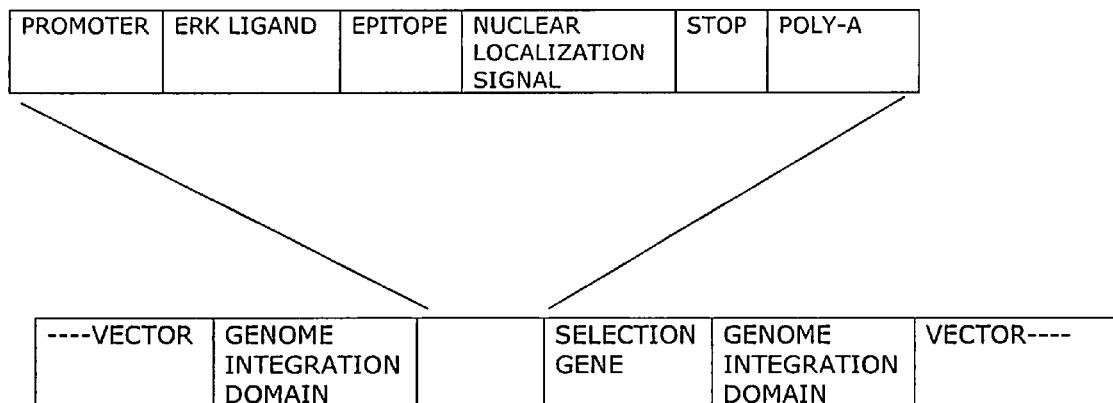
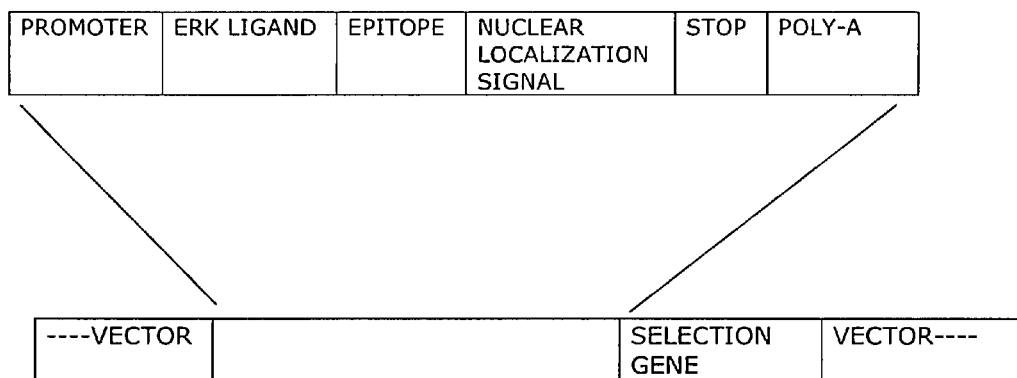
PROMOTER	LOCALIZATION SIGNAL	LIGAND or POLYLGAND	STOP	POLY-A
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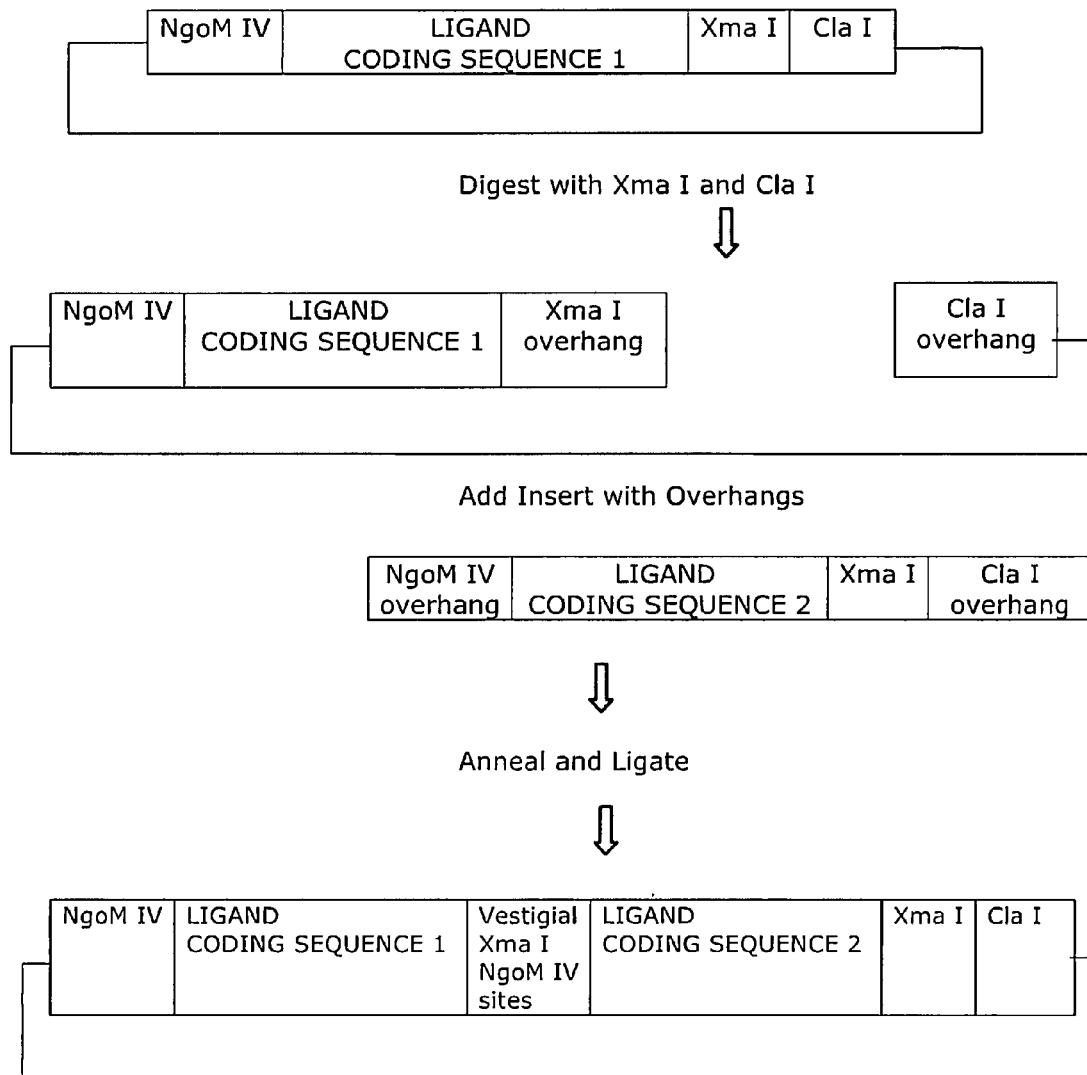
FIGURE 9F

PROMOTER	LIGAND or POLYLGAND	STOP	POLY-A
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FIGURE 9G



**FIGURE 10C****FIGURE 10D**

**FIGURE 11**

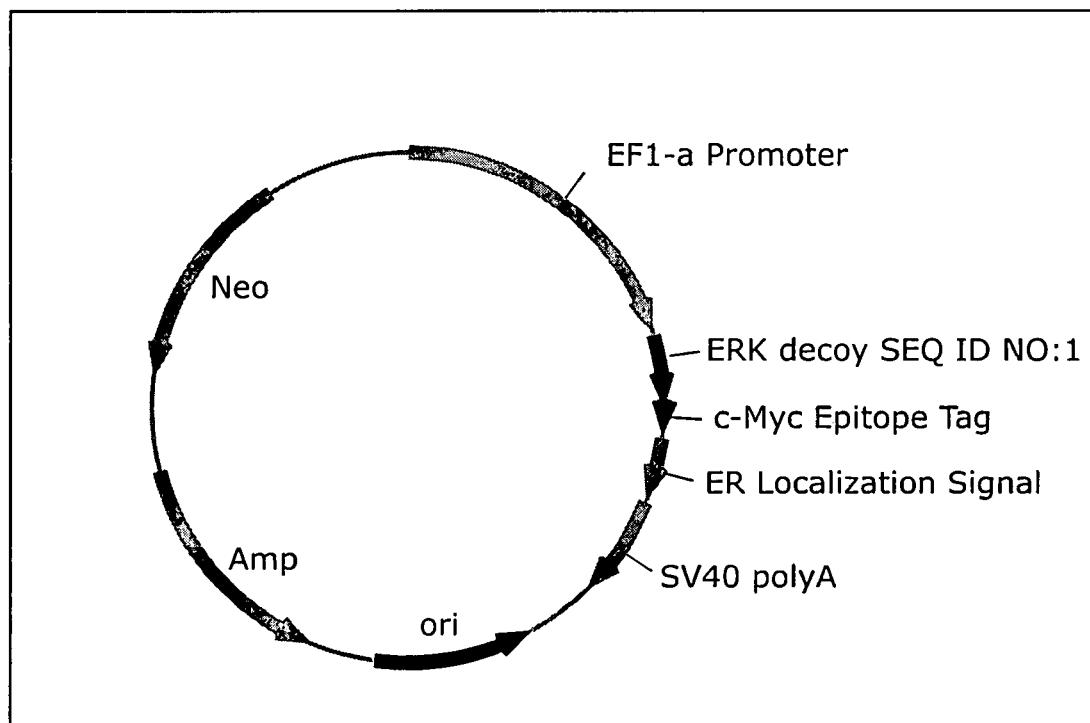


FIGURE 12

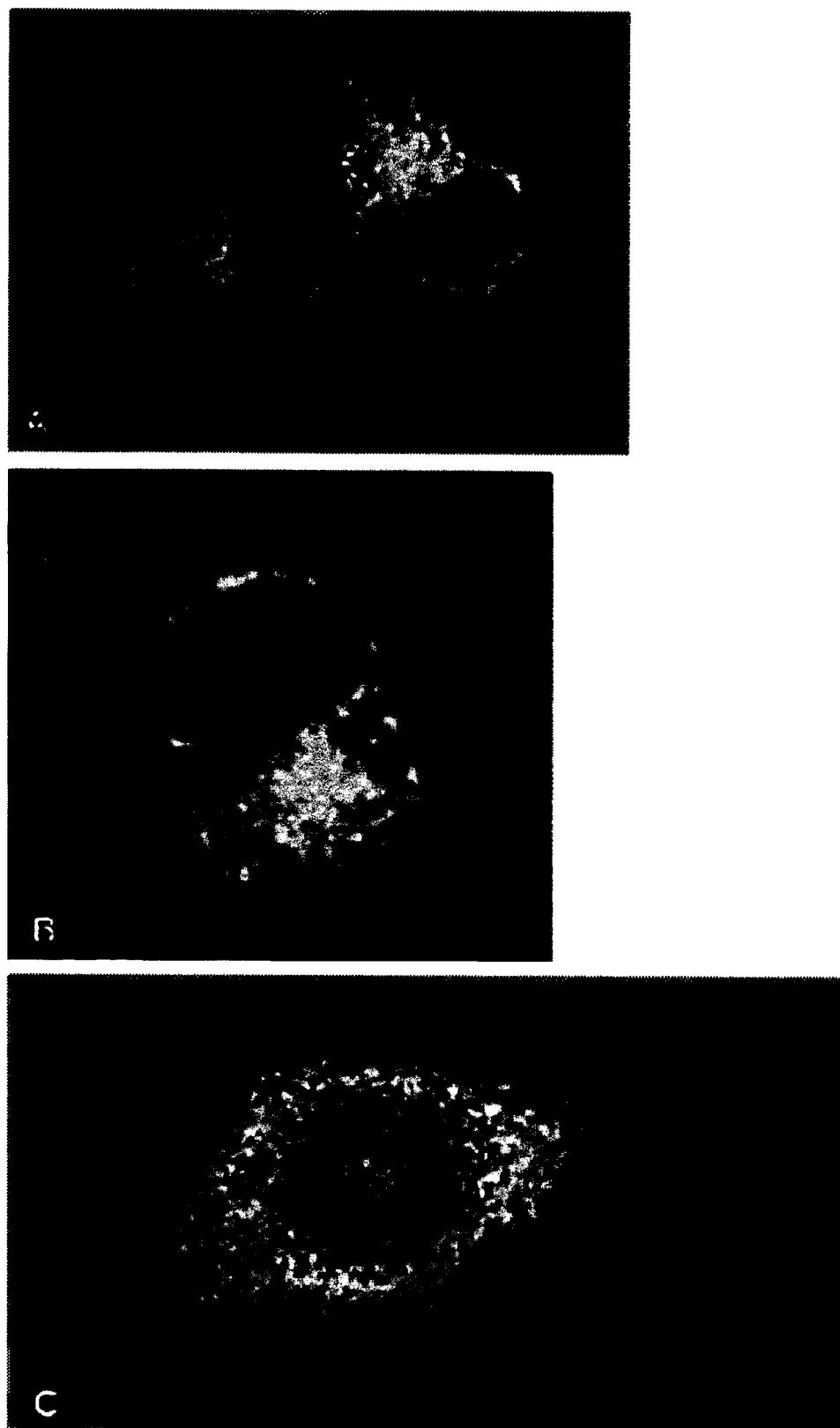


Figure 13

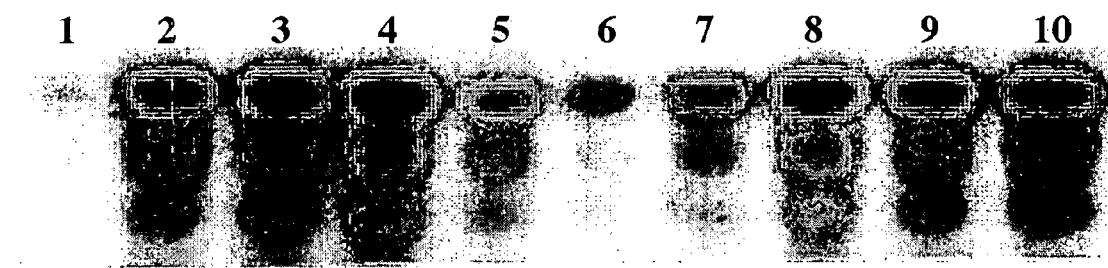


FIGURE 14

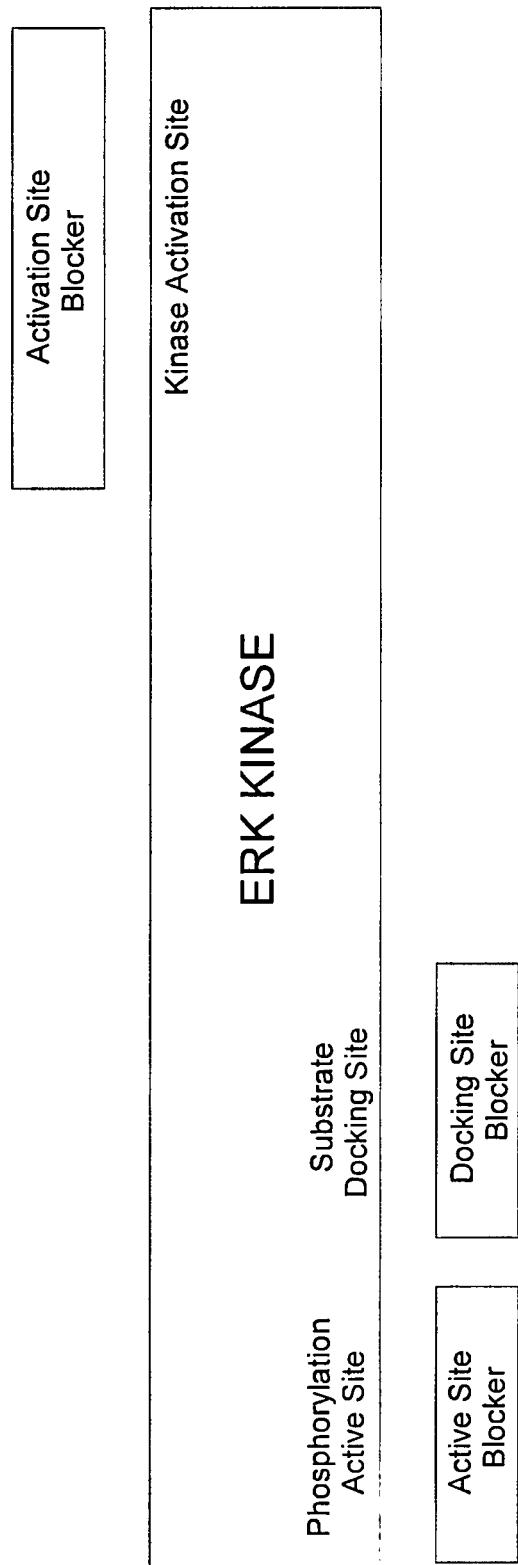


Figure 15

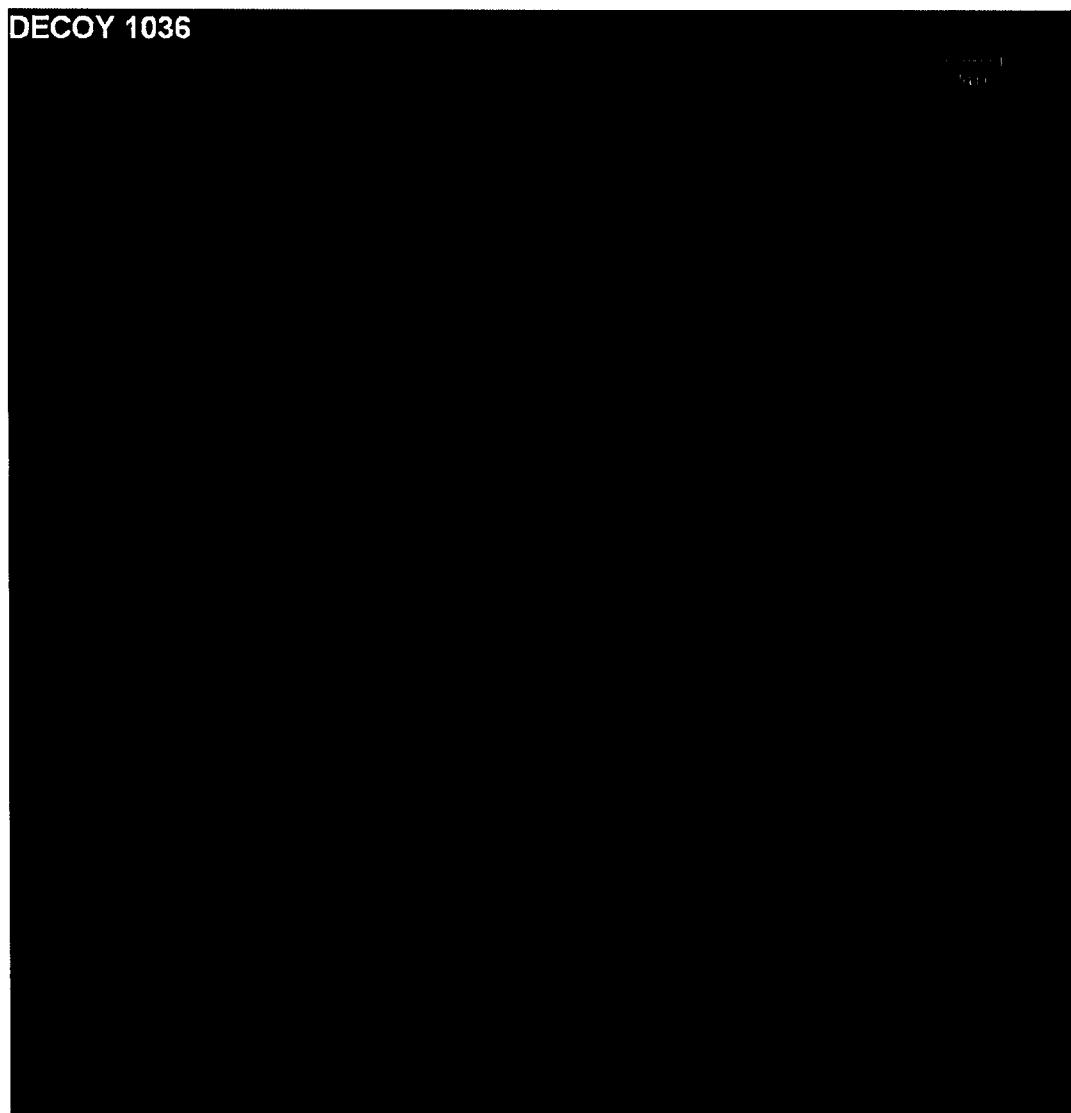


FIGURE 16

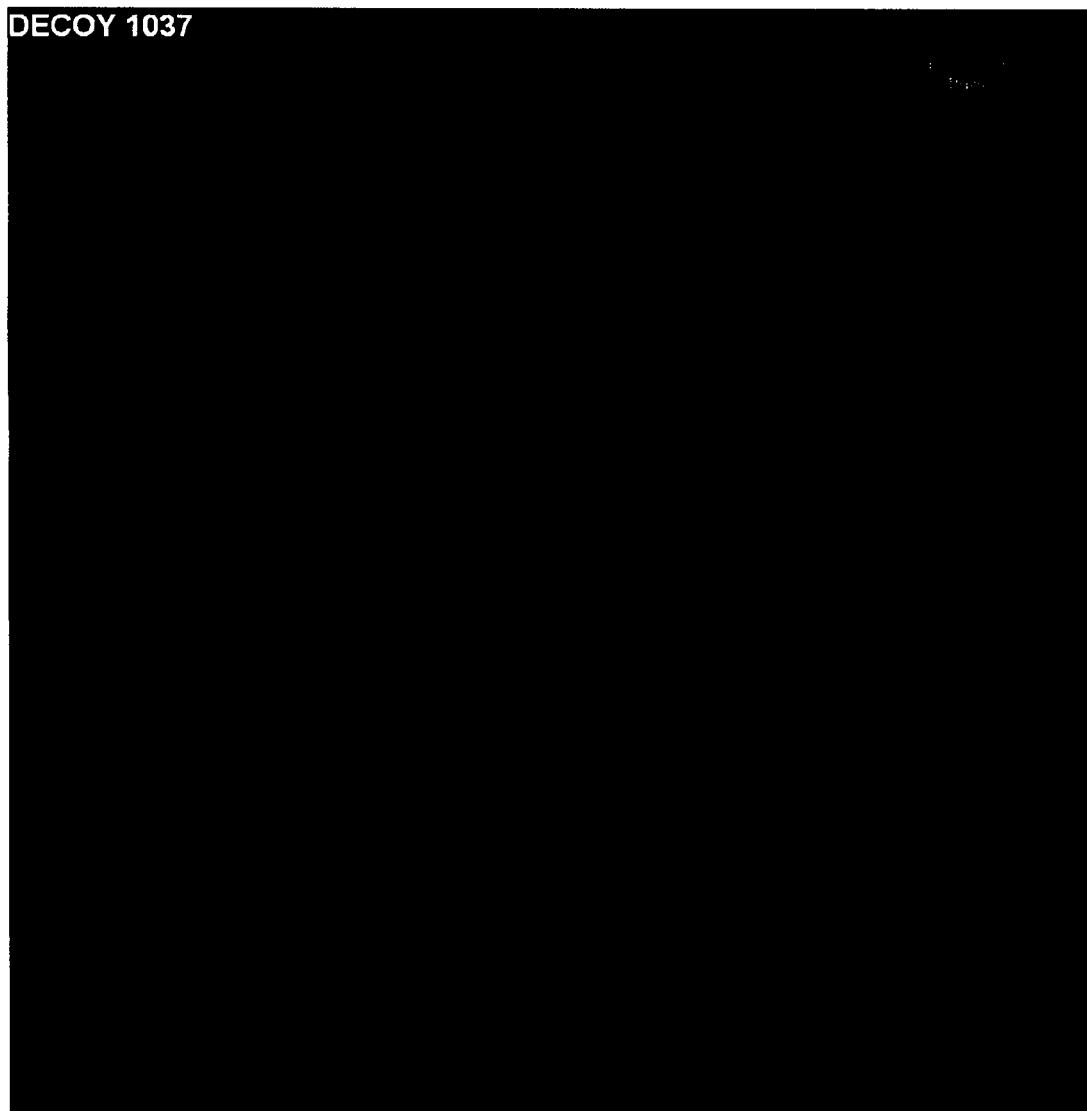


FIGURE 17

FIGURE 18

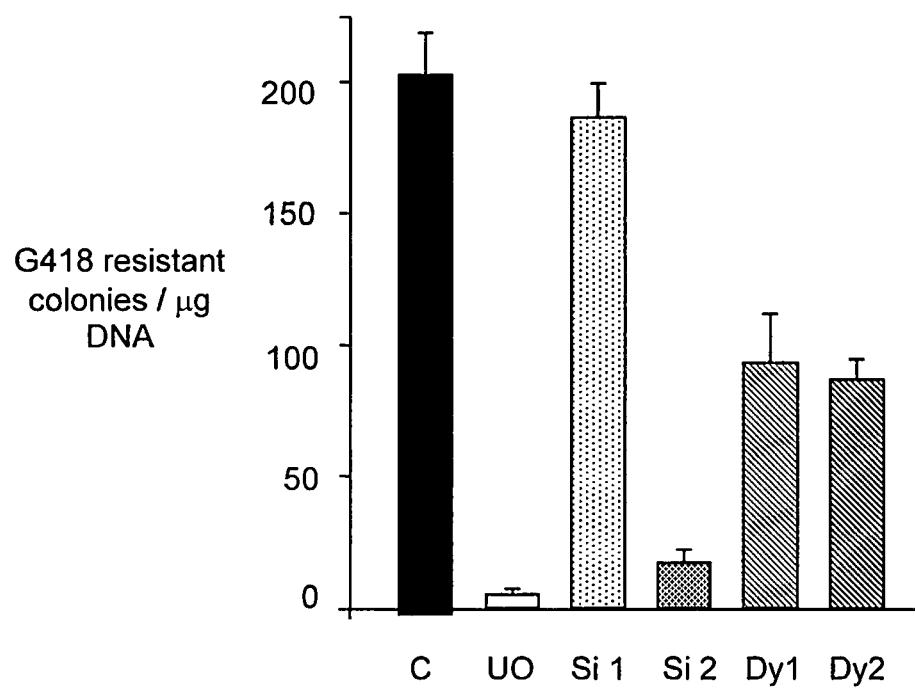
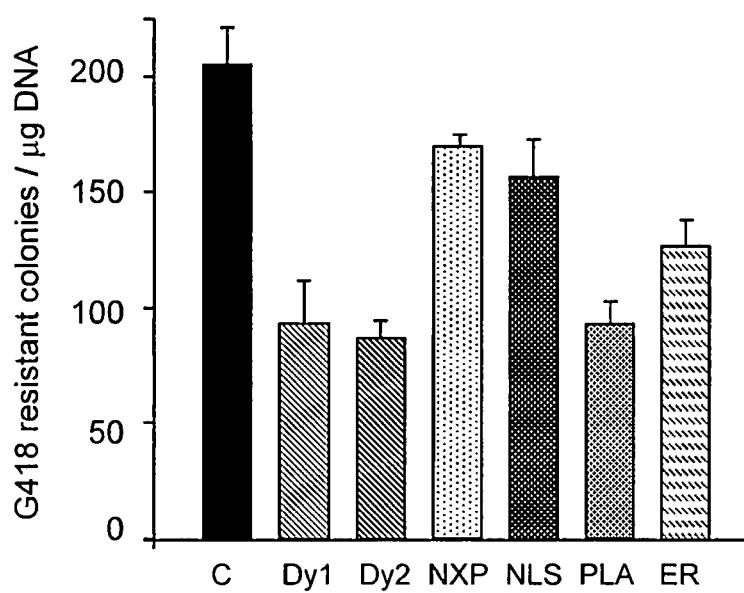


FIGURE 19



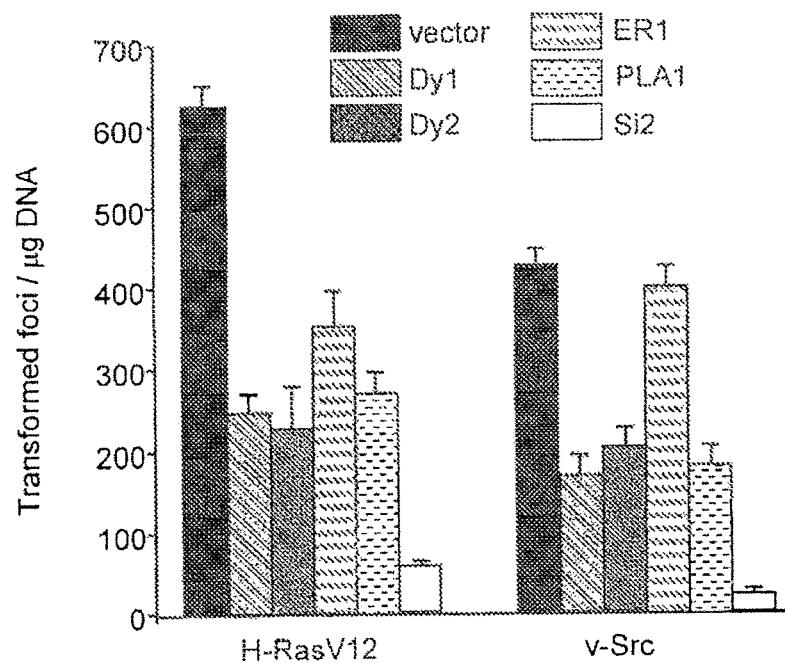


FIG. 20

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**POLYNUCLEOTIDES ENCODING
EXTRACELLULAR-SIGNAL-REGULATED
KINASE (ERK) HETEROPOLYLYGAND
POLYPEPTIDES**

This application claims benefit of priority to provisional application 60/865,589 filed 13 Nov. 2006.

**REFERENCE TO SEQUENCE LISTING
SUBMITTED ELECTRONICALLY VIA EFS-WEB**

This application includes a "SequenceListing—ascii.txt," 141,754 bytes, created on Sep. 12, 2013, and submitted electronically via EFS-Web, which is hereby incorporated by reference in its entirety.

FIELD OF INVENTION

The invention relates to mammalian kinase ligands, substrates and modulators. In particular, the invention relates to polypeptides, polypeptide compositions and polynucleotides that encode polypeptides that are ligands, substrates, and/or modulators of ERK. The invention also relates to polyligands that are homopolyligands or heteropolyligands that modulate ERK activity. The invention also relates to ligands and polyligands tethered to a subcellular location.

This application has subject matter related to application Ser. No. 10/724,532 (now U.S. Pat. No. 7,071,295), 10/682,764 (US2004/0185556, PCT/US2004/013517, WO2005/040336), Ser. No. 11/233,246, and US20040572011P (WO2005116231). Each of these patents and applications is hereby incorporated by reference.

BACKGROUND OF THE INVENTION

The ability to modulate protein activities has long been the hallmark of small molecule drug discovery and development, and the success of this traditional therapeutic approach is unquestioned. However, the number and nature of small molecule drug targets are more limiting than would be ideal and have less target specificity and more off-target side effects that will likely make for significant commercial and regulatory challenges in the years ahead. A newer technology for inhibiting protein activity that has received acceptance is siRNA-mediated gene silencing. The mechanism for siRNA inhibition is post-transcriptional and pre-translational. It has the advantage of being relatively selective for target RNA sequences but, like small molecules, suffers from off-target side effects.

Kinases are enzymes that catalyze the addition of phosphate to a molecule. The addition of phosphate by a kinase is called phosphorylation. When the kinase substrate is a protein molecule, the amino acids commonly phosphorylated are serine, threonine and tyrosine. Phosphatases are enzymes that remove phosphate from a molecule. The removal of phosphate is called dephosphorylation. Kinases and phosphatases often represent competing forces within a cell to transmit, attenuate, or otherwise modulate cellular signals and cellular control mechanisms. Kinases and phosphatases have both overlapping and unique natural substrates. Cellular signals and control mechanisms, as regulated by kinases, phosphatases, and their natural substrates are a target of research tool design and drug design.

Mammalian mitogen-activated protein kinase (MAPK) and extracellular-signal-regulated kinase (ERK) are the same enzyme, herein referred to as ERK. ERK has two isoforms, both of which can phosphorylate serine and threonine resi-

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dues in protein or peptide substrates. Use of the term ERK herein encompasses both ERK isoforms. Many cellular substrates of ERK have been identified. Furthermore, polypeptides have been used to examine ERK substrate specificity.

- 5 While polypeptides and variants thereof have been studied as individual substrates or ligands, mixed ligands linked together as polyligands that modulate ERK activity have not been demonstrated before this invention. An aspect of the invention is to provide novel, modular, inhibitors of ERK activity by modifying one or more natural substrates by truncation and/or by amino acid substitution. A further aspect of the invention is the subcellular localization of an ERK inhibitor, ligand, or polyligand by linking to a subcellular localization signal. Examples of ERK substrates and/or regulators 10 include those described in the following references: Adams, et al. 2000 J Neurochem 75:2277-87, Arnaud, et al. 2004 J Immunol 173:3962-71, Chung, et al. 1997 Mol Cell Biol 17:6508-16, Clark-Lewis, et al. 1991 J Biol Chem 266:15180-4, Eymen, et al. 2006 Cell Cycle 5:759-65, Fantz, 15 et al. 2001 J Biol Chem 276:27256-65, Garcia, et al. 2002 Embo J 21:5151-63, Gille, et al. 1995 Embo J 14:951-62, Haycock, et al. 1992 Proc Natl Acad Sci USA 89:2365-9, Hedges, et al. 2000 Am J Physiol Cell Physiol 278:C718-26, Hindley, et al. 2002 J Cell Sci 115:1575-81, Howell, et al. 20 1991 Mol Cell Biol 11:568-72, Ishibe, et al. 2004 Mol Cell 16:257-67, Jacobs, et al. 1999 Genes Dev 13:163-75, Jacque, et al. 1998 Embo J 17:2607-18, Kelemen, et al. 2002 J Biol Chem 277:8741-8, Kolch 2000 Biochem J 351 Pt 2:289-305, Lefebvre, et al. 2002 J Cell Biol 157:603-13, Lin, et al. 1999 25 J Biol Chem 274:15971-4, Matallanas, et al. 2006 Mol Cell Biol 26:100-16, Matsuura, et al. 2005 Biochemistry 44:12546-53, Matter, et al. 2002 Nature 420:691-5, Missero, et al. 2000 Mol Cell Biol 20:2783-93, Morton, et al. 2004 FEBS Lett 572:177-83, Pandey, et al. 2005 Mol Cell Biol 30 25:10695-710, Sanghera, et al. 1990 FEBS Lett 273:223-6, Schaeffer, et al. 1999 Mol Cell Biol 19:2435-44, Songyang, et al. 1996 Mol Cell Biol 16:6486-93, Soond, et al. 2005 J Cell Sci 118:2371-80, Tenet, et al. 2003 Development 130:5169-77, Veeranna, et al. 1998 J Neurosci 18:4008-21, Xu, et al. 40 2001 Mol Cell Biol 21:2981-90, Zhang, et al. 2001 J Biol Chem 276:14572-80, and MAP Kinase Substrate Peptide Catalog #2-125 Lot #23369 (Upstate, Lake Placid, N.Y.).

Design and synthesis of polypeptide ligands that modulate calcium/calmodulin-dependent protein kinase and that localize to the cardiac sarco(endo)plasmic reticulum was performed by Ji et al. (J Biol Chem (2003) 278:25063-71). Ji et al. accomplished this by generating expression constructs that localized calcium/calmodulin-dependent protein kinase inhibitory polypeptide ligands to the sarcoplasmic reticulum by fusing a sarcoplasmic reticulum localization signal derived from phospholamban to a polypeptide ligand. See also U.S. Pat. No. 7,071,295.

**DETAILED DESCRIPTION OF POLYPEPTIDE
AND POLYNUCLEOTIDE SEQUENCES**

SEQ ID NOS:1-8 are example polyligands and polynucleotides encoding them.

Specifically, the ERK polyligand of SEQ ID NO:1 is 60 encoded by SEQ ID NO:2, SEQ ID NO:3, and by SEQ ID NO:4, wherein the codons have been optimized for mammalian expression. SEQ ID NO:3 and SEQ ID NO:4 include different alternatives of predetermined flanking restriction sites. Furthermore, SEQ ID NO:4 utilizes alternative codons 65 for mammalian expression. A vector map of a vector containing SEQ ID NO:4 is shown in FIG. 12 (labeled ERK decoy). SEQ ID NO:1 is an embodiment of a polyligand of the struc-

ture A-S1-B-S2-C- S3-D-S4-E-S5-F, wherein A is SEQ ID NO:91, B is SEQ ID NO:97, C is SEQ ID NO:28, D is SEQ ID NO:29, E is SEQ ID NO:30, and F is SEQ ID NO:31, wherein Xaa is alanine, and wherein S1 is a spacer of the amino acid sequence AA, and S2 is a spacer of amino acid sequence AAAA (SEQ ID NO: 109), S3 is a spacer of the amino acid sequence GAGA (SEQ ID NO: 110), S4 is a spacer of the amino acid sequence GGGG (SEQ ID NO: 111), and S5 is a spacer of the amino acid sequence AGAG (SEQ ID NO: 112). A polyligand of structure A-S1-B-S2-C-S3-D-S4-E -S5-F is also called herein a heteropolyligand, shown generically in FIG. 4D.

SEQ ID NO:5 is an embodiment of a polyligand of the structure X-Y-S2-Z-S3-A-S4-B -S6-C-S5-D-S7-E-S8-F, wherein X is SEQ ID NO:32, Y is SEQ ID NO:98, Z is SEQ ID NO:33, A is SEQ ID NO:34, B is SEQ ID NO:35, C is SEQ ID NO:100, D is SEQ ID NO:36, E is SEQ ID NO:37, and F is SEQ ID NO:107, wherein Xaa is alanine, and wherein S2 is a spacer of amino acid sequence AAAA (SEQ ID NO: 109), S3 is a spacer of the amino acid sequence GAGA (SEQ ID NO: 110), S4 is a spacer of the amino acid sequence GGGG (SEQ ID NO: 111), S6 is a spacer of the amino acid sequence AGPGAEF (SEQ ID NO: 113), S5 is a spacer of the amino acid sequence AGAG (SEQ ID NO: 112), S7 is a spacer of the amino acid sequence AAGG (SEQ ID NO: 114), and S8 is a spacer of the amino acid sequence GGAA (SEQ ID NO: 115). The ERK polyligand of SEQ ID NO:5 is encoded by SEQ ID NO:6, SEQ ID NO:7 and by SEQ ID NO:8, wherein the codons have been optimized for mammalian expression. SEQ ID NO:7 and SEQ ID NO:8 include different alternatives of predetermined flanking restriction sites. Furthermore, SEQ ID NO:8 utilizes alternative codons for mammalian expression. A polyligand of structure X-Y-S2-Z-S3-A-S4-B-S6-C-S5-D-S7-E-S8-F is also called herein a heteropolyligand, shown generically in FIG. 4E.

SEQ ID NOS:9-27 are full length ERK protein substrates. These sequences have the following public database accession numbers: NP004032, NP001871, NP149129, NP001781, 075956, NP005220, NP536739, CAI17445, AAF65618, NP001006666, NP035353, NP062651, Q07666, AAL68976, NP644805, NP003174, Q15648, NP033411, and AAA42258. Each of the sequences represented by these accession numbers is incorporated by reference herein. In SEQ ID NOS:9-27, the positions of the amino acid(s) phosphorylatable by ERK are represented by Xaa. In wild-type proteins, Xaa is serine or threonine. In the ligands of the invention, Xaa is any amino acid.

SEQ ID NOS:28-90 are peptide sequences including subsequences of SEQ ID NOS:9-27, which represent examples of kinase active site blocker peptide ligand sequences where the location of the ERK phosphorylatable serine or threonine in the natural polypeptide is designated as Xaa.

SEQ ID NOS:91-108 are polypeptide inhibitors of ERK (see FIG. 15). Specifically, SEQ ID NOS:91-96 are ERK activation site blockers, and SEQ ID NOS:97-108 are ERK docking site blockers.

SEQ ID NOS:28-108 represent examples of monomeric polypeptide ligand sequences.

Amino acid sequences containing Xaa encompass polypeptides where Xaa is any amino acid.

DETAILED DESCRIPTION OF DRAWINGS

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

FIGS. 1A-1C show examples of homopolymeric ligands without spacers.

FIGS. 2A-2C show examples of homopolymeric ligands with spacers.

FIGS. 3A-3E show examples of heteropolymeric ligands without spacers.

FIGS. 4A-4F show examples of heteropolymeric ligands with spacers. In FIG. 4E, the abbreviation, S, stands for SPACER.

FIGS. 5A-5G show examples of ligands and polymeric ligands linked to an optional epitope tag.

FIGS. 6A-6G show examples of ligands and polymeric ligands linked to an optional reporter.

FIGS. 7A-7G show examples of ligands and polymeric ligands linked to an optional localization signal.

FIGS. 8A-8G show examples of ligands and polymeric ligands linked to an optional localization signal and an optional epitope tag.

FIGS. 9A-9G show examples of gene constructs where ligands and polyligands are linked to an optional localization signal, an optional epitope tag, and an optional reporter.

FIGS. 10A-10D show examples of vectors containing ligand gene constructs.

FIG. 11 shows an example of a sequential cloning process useful for combinatorial synthesis of polyligands.

FIG. 12 shows a diagram of a vector for cell transformation.

FIG. 13 shows Cos7 cells transformed with the vector depicted in FIG. 12, wherein the vector includes SEQ ID NO:4 which encodes the ERK polyligand of SEQ ID NO:1. This figure demonstrates endoplasmic reticulum (ER) localization of an ERK polyligand: Cos7 cells were transfected with vector containing an ER localization signal, a c-Myc epitope tag, and the ERK polyligand of SEQ ID NO:1 (ERK decoy). Panels A and B depict Cos7 cells transfected with the ERK decoy while Panel C depicts a Cos7 cell transfected with a localization signal control vector lacking an ERK polyligand. The cells in each panel were treated with a stain for the ER-resident protein calreticulin (red) as well as anti-c-Myc antibody staining specific to the c-Myc epitope tag (green). Panels A, B and C show concentrated protein expression to the endoplasmic reticulum as evidenced by the co-localization between both the ERK decoy and localization control with the ER-resident protein calreticulin (yellow).

FIG. 14 shows localized inhibition of ERK-mediated myelin basic protein phosphorylation by the ERK polyligand of SEQ ID NO:1 (decoy). A constitutively-active form of the RasV 12 protein, a known activator of MAPK signaling pathways, was used to activate ERK kinase in defined regions of Cos7 cells. Several fusion proteins as described by Matallanas et al. *Mol Cell Biol.* 2006 January; 26(1):100-116 (hereby incorporated by reference), were used to activate ERK kinase in specific subcellular compartments. The constitutively-active RasV12 protein promoted cell-wide activation of ERK. The Lck-RasV12 fusion protein activated ERK-protein associated with lipid rafts in or near the plasma membrane. The M1-RasV12 fusion protein activated ERK in the endoplasmic reticulum. Lane 1: control. Lane 2: ERK activity in cells expressing active Lck-RasV12 fusion protein. Lane 3: ERK activity in cells co-expressing active Lck-RasV12 fusion protein, and ERK decoy protein (ER localization signal, a c-Myc epitope tag, and the ERK polyligand of SEQ ID NO:1). Lane 4: ERK activity in cells co-expressing active Lck-RasV12 fusion protein, and CAT fragment-containing ER localization control protein. Lane 5: ERK activity in cells expressing active M1-RasV12 fusion protein. Lane 6: ERK activity in cells co-expressing active M1-RasV12 fusion

protein, and ERK decoy protein. Lane 7: ERK activity in cells co-expressing active M1-RasV12 fusion protein, and CAT fragment-containing ER localization control protein. Lane 8: ERK activity cells expressing active RasV12 protein. Lane 9: ERK activity in cells co-expressing active RasV12 fusion protein, and ERK decoy protein. Lane 10: ERK activity in cells co-expressing active RasV12 protein, and CAT fragment-containing ER localization control protein. This figure represents compartmentalized ERK activity in the plasma membrane (Lanes 2-4), in the endoplasmic reticulum (Lanes 5-7), and cell wide (Lanes 8-10) in Cos-7 cells. The bands on the gel represent varying phosphorylation states of ERK substrate, myelin basic protein (MBP); darker bands represent higher levels of ERK activity. When SEQ ID NO:1 was added to cells with ER-active ERK, ERK activity in the endoplasmic reticulum was reduced by approximately 60%. Again, Lane 1 is the control. Lanes 2-4 show activated ERK at the plasma membrane. Lanes 5-7 show activated ERK in the ER. Lanes 8-10 show activated ERK in the entire cell. Lanes 2, 5, & 8 show normal ERK activity. Lanes 3, 6, & 9 show ERK activity with co-expressed SEQ ID NO:1 fusion protein. Lanes 4, 7, & 10 show ERK activity with co-expressed control.

FIG. 15 shows a diagram of the ERK interaction sites of the different categories of ERK monomeric ligands including active site blockers, docking site blockers, and activation site blockers.

FIG. 16 shows nuclear localization of SEQ ID NO:1 fused to a nuclear localization signal and c-Myc epitope tag. Location was detected by immunostaining for c-Myc (green).

FIG. 17 shows cytoplasmic localization of SEQ ID NO:1 fused to a nuclear-exclusion localization signal and c-Myc epitope tag. Location was detected by immunostaining for c-Myc (green).

FIG. 18 shows inhibition of cell proliferation using ERK polyligands of SEQ ID NO:1 and SEQ ID NO:5 as compared to siRNA and a small molecule inhibitor. G418-resistant colony formation was assayed in NIH3T3 cells using siRNA specific for ERK1 or ERK2 isoforms; a small molecule inhibitor; and pancellular (no localization signal) polyligands of SEQ ID NO:1 and SEQ ID NO:5. G418-resistant colony formation was assayed in NIH3T3 cells transfected with vector (C) (1 µg) plus: siRNA oligonucleotides for ERK isoform 1 (Si1) or ERK isoform 2 (Si2) (25 ng); or vectors encoding for SEQ ID NO:1 (Dy1) or SEQ ID NO:5 (Dy2) (1 µg); or treated with the MEK inhibitor UO126 (1 µM). Colonies were stained and counted after 15 days in culture.

FIG. 19 shows inhibition of cell proliferation using localized ERK polyligand SEQ ID NO:1 fused to different localization signals. G418-resistant colony formation was assayed in NIH3T3 cells using pancellular SEQ ID NO:1 and SEQ ID NO:5, or SEQ ID NO:1 targeted to either the cytoplasm (NXP, nuclear exclusion), nucleus (NLS), plasma membrane (PLA), or endoplasmic reticulum (ER). G418-resistant colony formation was assayed in NIH3T3 cells transfected with vector (C) (1 µg) plus constructs (1 µg each) encoding for SEQ ID NO:1 (Dy1), SEQ ID NO:5, (Dy2) or SEQ ID NO:1 targeted to: cytoplasm (NXP), nucleus (NLS), plasma membrane (PLA), and endoplasmic reticulum (ER). Colonies were stained and counted after 15 days in culture.

FIG. 20 shows inhibition of cell transformation with pancellular SEQ ID NO:1 (Dy1), pancellular SEQ ID NO:5 (Dy2), and ER-localized SEQ ID NO:1 (ER1), and plasma membrane-localized SEQ ID NO:1 (PLA1) as compared to siRNA against ERK isoform 2 (Si2). Transformed foci for-

mation was assayed in NIH3T3 cells transfected with H-ras V12 or v-Src (0.25 ng) plus constructs (1 µg each).

BRIEF DESCRIPTION OF THE INVENTION

The invention relates to polypeptide ligands and polyligands for ERK. Various embodiments of the ERK ligands and polyligands are represented in SEQ ID NOS:1-108. More specifically, the invention relates to ligands, homopolyligands, and heteropolyligands that comprise any one or more of SEQ ID NOS:28-108. Additionally, the invention relates to ligands and polyligands comprising one or more subsequences of SEQ ID NOS:9-27 or any portion thereof. Furthermore, the invention relates to polyligands with at least about 80%, 85%, 90%, 95%, 96%, 97%, 98% and 99% sequence identity to a polyligand comprising one or more of SEQ ID NOS:28-108 or any portion thereof. Furthermore, the invention relates to polyligands with at least about 80%, 85%, 90%, 95%, 96%, 97%, 98% and 99% sequence identity to a polyligand comprising one or more subsequences of SEQ ID NOS:9-27.

Polyligands, which can be homopolyligands or heteropolyligands, are chimeric ligands composed of two or more monomeric polypeptide ligands. An example of a monomeric ligand is the polypeptide represented by SEQ ID NO:38, wherein Xaa is any amino acid. SEQ ID NO:38 is a selected subsequence of wild-type full length SEQ ID NO:9, wherein the amino acid corresponding to Xaa in the wild-type sequence is a serine or threonine phosphorylatable by ERK. An example of a homopolyligand is a polypeptide comprising a dimer or multimer of SEQ ID NO:38, wherein Xaa is any amino acid. An example of a heteropolyligand is a polypeptide comprising SEQ ID NO:28 and one or more of SEQ ID NOS:29-108, wherein Xaa is any amino acid. There are numerous ways to combine SEQ ID NOS:28-108 into homopolymeric or heteropolymeric ligands. Furthermore, there are numerous ways to combine additional subsequences of SEQ ID NOS:9-27 with each other and with SEQ ID NOS:28-108 to make polymeric ligands.

The polyligands of the invention optionally comprise spacer amino acids before, after, or between monomers. SEQ ID NO:1 is an embodiment of a polyligand of the structure A-S1-B-S2-C-S3-D-S4-E-S5-F, wherein A is SEQ ID NO:91, B is SEQ ID NO:97, C is SEQ ID NO:28, D is SEQ ID NO:29, E is SEQ ID NO:30, and F is SEQ ID NO:31, wherein Xaa is alanine, and wherein S1, S2, S3, S4 and S5 are spacers. This invention intends to capture all combinations of homopolyligands and heteropolyligands without limitation to the examples given above or below. In this description, use of the term "ligand(s)" encompasses monomeric ligands, polymeric ligands, homopolymeric ligands and/or heteropolymeric ligands.

Monomeric ligands can be categorized into types (FIG. 15). One type of monomeric ligand is a polypeptide where at least a portion of the polypeptide is capable of being recognized by ERK as a substrate or pseudosubstrate (active site blocker). The portion of the polypeptide capable of recognition is termed the recognition motif. In the present invention, recognition motifs can be natural or synthetic. Examples of recognition motifs are well known in the art and include, but are not limited to, naturally occurring ERK substrates and pseudosubstrate motifs (SEQ ID NOS:28-90 and subsequences of SEQ ID NOS:9-27 containing a recognition motif). Another type of monomeric ligand is a polypeptide where at least a portion of the polypeptide is capable of associating with ERK at a substrate or pseudosubstrate docking site (docking site blocker). A docking site type of mono-

meric ligand prevents ERK substrate phosphorylation by interfering with substrate association and alignment (SEQ ID NOS:97-108). Yet another type of monomeric ligand is a polypeptide where at least a portion of the polypeptide is capable of associating with ERK at ERK's activation site (SEQ ID NOS: 91-96), thereby blocking ERK activation (activation site blocker), thereby preventing ERK from phosphorylating a substrate.

A polymeric ligand comprises two or more monomeric ligands linked together.

A homopolymeric ligand is a polymeric ligand where each of the monomeric ligands is identical in amino acid sequence, except that a phosphorylatable residue may be substituted or modified in one or more of the monomeric ligands.

A heteropolymeric ligand is a polymeric ligand where some of the monomeric ligands do not have an identical amino acid sequence.

The ligands of the invention are optionally linked to additional molecules or amino acids that provide an epitope tag, a reporter, and/or a cellular localization signal. The cellular localization signal targets the ligands to a region of a cell. The epitope tag and/or reporter and/or localization signal may be the same molecule. The epitope tag and/or reporter and/or localization signal may also be different molecules.

The invention also encompasses polynucleotides comprising a nucleotide sequence encoding ligands, homopolyligands, and heteropolyligands. The nucleic acids of the invention are optionally linked to additional nucleotide sequences encoding polypeptides with additional features, such as an epitope tag, a reporter, and/or a cellular localization signal. The polynucleotides are optionally flanked by nucleotide sequences comprising restriction endonuclease sites and other nucleotides needed for restriction endonuclease activity. The flanking sequences optionally provide unique cloning sites within a vector and optionally provide directionality of subsequence cloning. Further, the nucleic acids of the invention are optionally incorporated into vector polynucleotides. The ligands, polyligands, and polynucleotides of this invention have utility as research tools and/or therapeutics.

Terms used in the specification and claims are intended to have meanings consistent with that known in the art. For example, as used herein, G418 is an aminoglycoside antibiotic also known as Geneticin. Resistance to G418 is conferred by the neo gene. HEK293 cells are human embryonic kidney 293 cell line. H-RasV12 is a constitutively active mutant form of Ras. NIH3T3 is a mouse fibroblast cell line. Raf stand for Ras-activated factor. Ras is a small GTPase or G protein. RNA stands for ribonucleic acid. SirNA stands for small interfering RNA. Transfection is the introduction of foreign material (such as DNA) into eukaryotic cells. Transformation is a process of tumorigenesis whereby normal cells become cancerous and possess phenotypes including but not limited to excessive growth, plasticity, chromosome abnormalities, foci formation, cell cycle abnormalities, among others. V-Src is a tyrosine kinase encoded by the viral oncogene isolated from Rous sarcoma virus.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to ligands and polyligands that are ERK modulators. Various embodiments of ligands and polyligands are represented in SEQ ID NOS:1-108. Polyligands are chimeric ligands comprising two or more monomeric polypeptide ligands. An example of a monomeric ligand is the polypeptide represented by SEQ ID NO:43, wherein Xaa is any amino acid. SEQ ID NO:43 is a selected subsequence of wild-type full length SEQ ID NO:11, wherein

the amino acid corresponding to Xaa in the wild-type sequence is a serine or threonine phosphorylatable by ERK. Another example of a monomeric ligand is the polypeptide represented by SEQ ID NO:99. Another example of a monomeric ligand is the polypeptide represented by SEQ ID NO:94. Each of SEQ ID NOS:28-108 represents an individual polypeptide ligand in monomeric form, wherein Xaa is any amino acid. SEQ ID NOS:28-90 are selected examples of subsequences of SEQ ID NOS:9-27, however, other subsequences of SEQ ID NOS:9-27 containing a recognition motif may also be utilized as monomeric ligands. Monomeric ligand subsequences of SEQ ID NOS:9-27 may be wild-type subsequences. Additionally, monomeric ligand subsequences of SEQ ID NOS:9-27 may have the ERK phosphorylatable amino acids replaced by other amino acids. Furthermore, monomeric ligands and polyligands may have at least about 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% sequence identity to a ligand comprising an amino acid sequence in one or more of SEQ ID NOS:28-108. Furthermore, monomeric ligands and polyligands may have at least about 80%, 85%, 90%, 95%, 96%, 97%, 98% and 99% sequence identity to a subsequence of SEQ ID NOS:9-27.

An example of a homopolyligand is a polypeptide comprising a dimer or multimer of SEQ ID NO:86, wherein Xaa is any amino acid. Another example of a homopolyligand is a polypeptide comprising a dimer or multimer of SEQ ID NO:95. Another example of a homopolyligand is a polypeptide comprising a dimer or multimer of SEQ ID NO:106.

An example of a heteropolyligand is a polypeptide comprising SEQ ID NO:108 and one or more of SEQ ID NOS: 28-107, wherein Xaa is any amino acid. There are numerous ways to combine SEQ ID NOS:28-108 into homopolymeric or heteropolymeric ligands. Furthermore, there are numerous ways to combine additional subsequences of SEQ ID NOS: 9-27 with each other and with SEQ ID NOS:28-108 to make polymeric ligands.

Polyligands may comprise any two or more of SEQ ID NOS:28-108, wherein Xaa is any amino acid. A dimer or multimer of SEQ ID NO:91 is an example of a homopolyligand. An example of a heteropolyligand is a polypeptide comprising SEQ ID NO:28 and one or more of SEQ ID NOS:29-108. There are numerous ways to combine SEQ ID NOS:28-108 into homopolymeric or heteropolymeric ligands. SEQ ID NOS:28-90 are selected examples of subsequences of SEQ ID NOS:9-27, however, additional subsequences, wild-type or mutated, may be utilized to form polyligands. The instant invention is directed to all possible combinations of homopolyligands and heteropolyligands without limitation.

SEQ ID NOS:9-27 show proteins that contain at least one serine or threonine residue phosphorylatable by ERK, the positions of which are represented by Xaa. SEQ ID NOS:28-90 are subsequences of SEQ ID NOS:9-27 where, again, the locations of the ERK phosphorylatable residues are represented by Xaa. In nature, Xaa is, generally speaking, serine or threonine. In one embodiment of the instant invention, Xaa can be any amino acid. Ligands where Xaa is serine or threonine can be used as part of a polyligand, however in one embodiment, at least one phosphorylatable serine or threonine is replaced with another amino acid, such as one of the naturally occurring amino acids including, alanine, aspartate, asparagine, cysteine, glutamate, glutamine, phenylalanine, glycine, histidine, isoleucine, leucine, lysine, methionine, proline, arginine, valine, tryptophan, or tyrosine. The Xaa may also be a non-naturally occurring amino acid. In another embodiment, the ERK phosphorylatable serine(s) or threonine(s) are replaced by alanine. The ligands and polyligands

of the invention are designed to modulate the endogenous effects of one or more isoforms of ERK.

In general, ligand monomers based on natural ERK substrates are built by isolating a putative ERK phosphorylation recognition motif in a ERK substrate. Sometimes it is desirable to modify the phosphorylatable residue to an amino acid other than serine or threonine. Additional monomers include the ERK recognition motif as well as amino acids adjacent and contiguous on either side of the ERK recognition motif. Monomeric ligands may therefore be any length provided the monomer includes the ERK recognition motif. For example, the monomer may comprise an ERK recognition motif and at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30-100 or more amino acids adjacent to the recognition motif.

For example, in one embodiment, the invention comprises an inhibitor of ERK comprising at least one copy of a peptide selected from the group consisting of:

- a) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 407-415 of SEQ ID NO:9, wherein the amino acid residue corresponding to amino acid residue 412 of SEQ ID NO:9 is an amino acid residue other than serine or threonine;
- b) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 403-416 of SEQ ID NO:9, wherein the amino acid residue corresponding to amino acid residue 412 of SEQ ID NO:9 is an amino acid residue other than serine or threonine;
- c) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 400-417 of SEQ ID NO:9, wherein the amino acid residue corresponding to amino acid residue 412 of SEQ ID NO:9 is an amino acid residue other than serine or threonine; and
- d) a peptide at least 80% identical to a peptide comprising amino acid residues corresponding to amino acid residues 399-418 of SEQ ID NO:9, wherein the amino acid residue corresponding to amino acid residue 412 of SEQ ID NO:9 is an amino acid residue other than serine or threonine.

As used herein, the terms "correspond(s) to" and "corresponding to," as they relate to sequence alignment, are intended to mean enumerated positions within a reference protein, e.g., CDC25c (SEQ ID NO:12), and those positions that align with the positions on the reference protein. Thus, when the amino acid sequence of a subject peptide is aligned with the amino acid sequence of a reference peptide, e.g., SEQ ID NO:12, the amino acids in the subject peptide sequence that "correspond to" certain enumerated positions of the reference peptide sequence are those that align with these positions of the reference peptide sequence, but are not necessarily in these exact numerical positions of the reference sequence. Methods for aligning sequences for determining corresponding amino acids between sequences are described below.

Additional embodiments of the invention include monomers (as described above) based on any putative or real substrate for ERK, such as substrates identified by SEQ ID NOS: 9-27. Furthermore, if the substrate has more than one recognition motif, then more than one monomer may be identified therein.

Further embodiments of the invention include monomers based on ERK inhibitors, regulators, or binding partners, such as those identified by SEQ ID NOS:91-108 (ERK activation site blockers and ERK substrate docking site blockers) and subsequences thereof.

Another embodiment of the invention is a nucleic acid molecule comprising a polynucleotide sequence encoding at least one copy of a ligand peptide.

Another embodiment of the invention is a nucleic acid molecule wherein the polynucleotide sequence encodes one or more copies of one or more peptide ligands.

Another embodiment of the invention is a nucleic acid molecule wherein the polynucleotide sequence encodes at least a number of copies of the peptide selected from the group consisting of 2, 3, 4, 5, 6, 7, 8, 9 or 10.

Another embodiment of the invention is a vector comprising a nucleic acid molecule encoding at least one copy of a ligand or polyligand.

Another embodiment of the invention is a recombinant host cell comprising a vector comprising a nucleic acid molecule encoding at least one copy of a ligand or polyligand.

Another embodiment of the invention is a method of inhibiting ERK in a cell comprising transfecting a vector comprising a nucleic acid molecule encoding at least one copy of a ligand or polyligand into a host cell and culturing the transfected host cell under conditions suitable to produce at least one copy of the ligand or polyligand.

The invention also relates to modified inhibitors that are at least about 80%, 85%, 90% 95%, 96%, 97%, 98% or 99% identical to a reference inhibitor. A "modified inhibitor" is used to mean a peptide that can be created by addition, deletion or substitution of one or more amino acids in the primary structure (amino acid sequence) of a inhibitor protein or polypeptide. A "modified recognition motif" is a naturally occurring ERK recognition motif that has been modified by addition, deletion, or substitution of one or more amino acids in the primary structure (amino acid sequence) of the motif.

For example, a modified ERK recognition motif may be a motif where the phosphorylatable amino acid has been modified to a non-phosphorylatable amino acid. The terms "protein" and "polypeptide" are used interchangeably herein. The reference inhibitor is not necessarily a wild-type protein or a portion thereof. Thus, the reference inhibitor may be a protein or peptide whose sequence was previously modified over a wild-type protein. The reference inhibitor may or may not be the wild-type protein from a particular organism.

A polypeptide having an amino acid sequence at least, for example, about 95% "identical" to a reference an amino acid sequence is understood to mean that the amino acid sequence of the polypeptide is identical to the reference sequence except that the amino acid sequence may include up to about five modifications per each 100 amino acids of the reference amino acid sequence encoding the reference peptide. In other words, to obtain a peptide having an amino acid sequence at least about 95% identical to a reference amino acid sequence, up to about 5% of the amino acid residues of the reference sequence may be deleted or substituted with another amino acid or a number of amino acids up to about 5% of the total amino acids in the reference sequence may be inserted into the reference sequence. These modifications of the reference sequence may occur at the N-terminus or C-terminus positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among amino acids in the reference sequence or in one or more contiguous groups within the reference sequence.

As used herein, "identity" is a measure of the identity of nucleotide sequences or amino acid sequences compared to a reference nucleotide or amino acid sequence. In general, the sequences are aligned so that the highest order match is obtained. "Identity" per se has an art-recognized meaning and can be calculated using published techniques. (See, e.g., Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York (1988); Biocomputing: Informatics And Genome Projects, Smith, D. W., ed., Academic Press,

New York (1993); Computer Analysis of Sequence Data, Part 1, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey (1994); von Heinje, G., Sequence Analysis In Molecular Biology, Academic Press (1987); and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York (1991)). While there exist several methods to measure identity between two polynucleotide or polypeptide sequences, the term “identity” is well known to skilled artisans (Carillo, H. & Lipton, D., Siam J Applied Math 48:1073 (1988)). Methods commonly employed to determine identity or similarity between two sequences include, but are not limited to, those disclosed in Guide to Huge Computers, Martin J. Bishop, ed., Academic Press, San Diego (1994) and Carillo, H. & Lipton, D., Siam J Applied Math 48:1073 (1988). Computer programs may also contain methods and algorithms that calculate identity and similarity. Examples of computer program methods to determine identity and similarity between two sequences include, but are not limited to, GCG program package (Devereux, J., et al., Nucleic Acids Research 12(i):387 (1984)), BLASTP, ExPASy, BLASTN, FASTA (Atschul, S. F., et al., J Molec Biol 215:403 (1990)) and FASTDB. Examples of methods to determine identity and similarity are discussed in Michaels, G. and Garian, R., Current Protocols in Protein Science, Vol 1, John Wiley & Sons, Inc. (2000), which is incorporated by reference. In one embodiment of the present invention, the algorithm used to determine identity between two or more polypeptides is BLASTP.

In another embodiment of the present invention, the algorithm used to determine identity between two or more polypeptides is FASTDB, which is based upon the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990), incorporated by reference). In a FASTDB sequence alignment, the query and subject sequences are amino sequences. The result of sequence alignment is in percent identity. Parameters that may be used in a FASTDB alignment of amino acid sequences to calculate percent identity include, but are not limited to: Matrix=PAM, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject amino sequence, whichever is shorter.

If the subject sequence is shorter or longer than the query sequence because of N-terminus or C-terminus additions or deletions, not because of internal additions or deletions, a manual correction can be made, because the FASTDB program does not account for N-terminus and C-terminus truncations or additions of the subject sequence when calculating percent identity. For subject sequences truncated at both ends, relative to the query sequence, the percent identity is corrected by calculating the number of amino acids of the query sequence that are N- and C-terminus to the reference sequence that are not matched/aligned, as a percent of the total amino acids of the query sequence. The results of the FASTDB sequence alignment determine matching/alignment. The alignment percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score can be used for the purposes of determining how alignments “correspond” to each other, as well as percentage identity. Residues of the query (subject) sequences or the reference sequence that extend past the N- or C-termini of the reference or subject sequence, respectively, may be considered for the purposes of manually adjusting the percent identity score. That is, residues that are not matched/aligned with the N- or C-termini of the compari-

son sequence may be counted when manually adjusting the percent identity score or alignment numbering.

For example, a 90 amino acid residue subject sequence is aligned with a 100 residue reference sequence to determine 5 percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a match/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the 10 sequence (number of residues at the N- and C-termini not matched/total number of residues in the query sequence) so 10 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared 15 with a 100 reference sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected.

The polyligands of the invention optionally comprise 20 spacer amino acids before, after, or between monomers. The length and composition of the spacer may vary. An example of a spacer is glycine, alanine, polyglycine, or polyalanine. Specific examples of spacers used between monomers in 25 SEQ ID NO:5 are the four amino acid spacers AAAA (SEQ ID NO:109), GAGA (SEQ Id NO:110), GGGG (SEQ ID NO:111), AGAG (SEQ ID NO:112), AAGG (SEQ ID NO:114), GGAA (SEQ ID NO:115), and the six amino acid spacer AGPGAEF (SEQ ID NO:113). In the instance of SEQ 30 ID NO:5, the proline-containing spacer is intended to break an alpha helical secondary structure. Spacer amino acids may be any amino acid and are not limited to alanine, glycine and proline. The instant invention is directed to all combinations of homopolyligands and heteropolyligands, with or without spacers, and without limitation to the examples given above or below.

The ligands and polyligands of the invention are optionally linked to additional molecules or amino acids that provide an 40 epitope tag, a reporter, and/or localize the ligand to a region of a cell (See FIGS. 5A-5G, FIGS. 6A-6G, FIGS. 7A-7G, and FIGS. 8A-8G). Non-limiting examples of epitope tags are FLAG™ (Kodak; Rochester, N.Y.), HA (hemagglutinin), c-Myc and His6. Non-limiting examples of reporters are alkaline phosphatase, galactosidase, peroxidase, luciferase and green fluorescent protein (GFP). Non-limiting examples of cellular localizations are sarcoplasmic reticulum, endoplasmic reticulum, mitochondria, golgi apparatus, nucleus, plasma membrane, apical membrane, and basolateral membrane. The epitopes, reporters and localization signals are given by 45 way of example and without limitation. The epitope tag, reporter and/or localization signal may be the same molecule. The epitope tag, reporter and/or localization signal may also be different molecules.

Ligands and polyligands and optional amino acids linked 50 thereto can be synthesized chemically or recombinantly using techniques known in the art. Chemical synthesis techniques include but are not limited to peptide synthesis which is often performed using an automated peptide synthesizer. Peptides can also be synthesized utilizing non-automated peptide synthesis methods known in the art. Recombinant techniques include insertion of ligand-encoding nucleic acids into expression vectors, wherein nucleic acid expression products are synthesized using cellular factors and processes.

Linkage of a cellular localization signal, epitope tag, or 55 reporter to a ligand or polyligand can include covalent or enzymatic linkage to the ligand. When the localization signal comprises material other than a polypeptide, such as a lipid or

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carbohydrate, a chemical reaction to link molecules may be utilized. Additionally, non-standard amino acids and amino acids modified with lipids, carbohydrates, phosphate or other molecules may be used as precursors to peptide synthesis. The ligands of the invention have therapeutic utility with or without localization signals. However, ligands linked to localization signals have utility as subcellular tools or therapeutics. For example, ligands depicted generically in FIGS. 7A-7G represent ligands with utility as subcellular tools or therapeutics. ERK ligand-containing gene constructs are also delivered via gene therapy. FIGS. 10B and 10C depict embodiments of gene therapy vectors for delivering and controlling polypeptide expression *in vivo*. Polynucleotide sequences linked to the gene construct in FIGS. 10B and 10C include genome integration domains to facilitate integration of the transgene into a viral genome and/or host genome.

FIG. 10A shows a vector containing an ERK ligand gene construct, wherein the ligand gene construct is releasable from the vector as a unit useful for generating transgenic animals. For example, the ligand gene construct, or transgene, is released from the vector backbone by restriction endonuclease digestion. The released transgene is then injected into pronuclei of fertilized mouse eggs; or the transgene is used to transform embryonic stem cells. The vector containing a ligand gene construct of FIG. 10A is also useful for transient transfection of the transgene, wherein the promoter and codons of the transgene are optimized for the host organism. The vector containing a ligand gene construct of FIG. 10A is also useful for recombinant expression of polypeptides in fermentable organisms adaptable for small or large scale production, wherein the promoter and codons of the transgene are optimized for the fermentation host organism.

FIG. 10D shows a vector containing an ERK ligand gene construct useful for generating stable cell lines.

The invention also encompasses polynucleotides comprising nucleotide sequences encoding ligands, homopolyligands, and heteropolyligands. The polynucleotides of the invention are optionally linked to additional nucleotide sequences encoding epitopes, reporters and/or localization signals. Further, the nucleic acids of the invention are optionally incorporated into vector polynucleotides. The polynucleotides are optionally flanked by nucleotide sequences comprising restriction endonuclease sites and other nucleotides needed for restriction endonuclease activity. The flanking sequences optionally provide cloning sites within a vector. The restriction sites can include, but are not limited to, any of the commonly used sites in most commercially available cloning vectors. Examples of such sites are those recognized by BamHI, ClaI, EcoRI, EcoRV, Spel, Anil, NdeI, NheI, XbaI, XhoI, SphI, NaeI, SexAI, HindIII, HpaI, and PstI restriction endonucleases. Sites for cleavage by other restriction enzymes, including homing endonucleases, are also used for this purpose. The polynucleotide flanking sequences also optionally provide directionality of subsequence cloning. It is preferred that 5' and 3' restriction endonuclease sites differ from each other so that double-stranded DNA can be directionally cloned into corresponding complementary sites of a cloning vector.

Ligands and polyligands with or without localization signals, epitopes or reporters are alternatively synthesized by recombinant techniques. Polynucleotide expression constructs are made containing desired components and inserted into an expression vector. The expression vector is then transfected into cells and the polypeptide products are expressed and isolated. Ligands made according to recombinant DNA techniques have utility as research tools and/or therapeutics.

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The following is an example of how polynucleotides encoding ligands and polyligands are produced. Complementary oligonucleotides encoding the ligands and flanking sequences are synthesized and annealed. The resulting double-stranded DNA molecule is inserted into a cloning vector using techniques known in the art. When the ligands and polyligands are placed in-frame adjacent to sequences within a transgenic gene construct that is translated into a protein product, they form part of a fusion protein when expressed in cells or transgenic animals.

Another embodiment of the invention relates to selective control of transgene expression in a desired cell or organism. The promotor portion of the recombinant gene can be a constitutive promotor, a non-constitutive promotor, a tissue-specific promotor (constitutive or non-constitutive) or a selectively controlled promotor. Different selectively controlled promotors are controlled by different mechanisms. For example, RHEOSWITCH is an inducible promotor system available from New England Biolabs (Ipswich, Mass.). Temperature sensitive promotors can also be used to increase or decrease gene expression. An embodiment of the invention comprises a ligand or polyligand gene construct whose expression is controlled by an inducible promotor. In one embodiment, the inducible promotor is tetracycline controllable.

Polyligands are modular in nature. An aspect of the instant invention is the combinatorial modularity of the disclosed polyligands. Another aspect of the invention are methods of making these modular polyligands easily and conveniently. In this regard, an embodiment of the invention comprises methods of modular subsequence cloning of genetic expression components. When the ligands, homopolyligands, heteropolyligands and optional amino acid expression components are synthesized recombinantly, one can consider each clonable element as a module. For speed and convenience of cloning, it is desirable to make modular elements that are compatible at cohesive ends and are easy to insert and clone sequentially. This is accomplished by exploiting the natural properties of restriction endonuclease site recognition and cleavage. One aspect of the invention encompasses module flanking sequences that, at one end of the module, are utilized for restriction enzyme digestion once, and at the other end, utilized for restriction enzyme digestion as many times as desired. In other words, a restriction site at one end of the module is utilized and destroyed in order to effect sequential cloning of modular elements. An example of restriction sites flanking a coding region module are sequences recognized by the restriction enzymes NgoM IV and Cla I; or Xma I and Cla I. Cutting a first circular DNA with NgoM IV and Cla I to yield linear DNA with a 5' NgoM IV overhang and a 3' Cla I overhang; and cutting a second circular DNA with Xma I and Cla I to yield linear DNA with a 5' Cla I overhang and a 3' Xma I overhang generates first and second DNA fragments with compatible cohesive ends. When these first and second DNA fragments are mixed together, annealed, and ligated to form a third circular DNA fragment, the NgoM IV site that was in the first DNA and the Xma I site that was in the second DNA are destroyed in the third circular DNA. Now this vestigial region of DNA is protected from further Xma I or NgoM IV digestion, but flanking sequences remaining in the third circular DNA still contain intact 5' NgoM IV and 3' Cla I sites. This process can be repeated numerous times to achieve directional, sequential, modular cloning events. Restriction sites recognized by NgoM IV, Xma I, and Cla I endonucleases represent a group of sites that permit sequential cloning when used as flanking sequences.

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Another way to assemble coding region modules directionally and sequentially employs linear DNA in addition to circular DNA. For example, like the sequential cloning process described above, restriction sites flanking a coding region module are sequences recognized by the restriction enzymes NgoM IV and Cla I; or Xma I and Cla I. A first circular DNA is cut with NgoM IV and Cla I to yield linear DNA with a 5' NgoM IV overhang and a 3' Cla I overhang. A second linear double-stranded DNA is generated by PCR amplification or by synthesizing and annealing complimentary oligonucleotides. The second linear DNA has 5' Cla I overhang and a 3' Xma I overhang, which are compatible cohesive ends with the first DNA linearized. When these first and second DNA fragments are mixed together, annealed, and ligated to form a third circular DNA fragment, the NgoM IV site that was in the first DNA and the Xma I site that was in the second DNA are destroyed in the third circular DNA. Flanking sequences remaining in the third circular DNA still contain intact 5' NgoM IV and 3' Cla I sites. This process can be repeated numerous times to achieve directional, sequential, modular cloning events. Restriction sites recognized by NgoM IV, Xma I, and Cla I endonucleases represent a group of sites that permit sequential cloning when used as flanking sequences. This process is depicted in FIG. 11.

One of ordinary skill in the art recognizes that other restriction site groups can accomplish sequential, directional cloning as described herein. Preferred criteria for restriction endonuclease selection are selecting a pair of endonucleases that generate compatible cohesive ends but whose sites are destroyed upon ligation with each other. Another criteria is to select a third endonuclease site that does not generate sticky ends compatible with either of the first two. When such criteria are utilized as a system for sequential, directional cloning, ligands, polyligands and other coding regions or expression components can be combinatorially assembled as desired. The same sequential process can be utilized for epitope, reporter, and/or localization signals.

Polyligands and methods of making polyligands that modulate ERK activity are disclosed. Therapeutics include delivery of purified ligand or polyligand with or without a localization signal to a cell. Alternatively, ligands and polyligands with or without a localization signals are delivered via adenovirus, lentivirus, adeno-associated virus, or other viral constructs that express protein product in a cell.

Methods

Assays. Ligands of the invention are assayed for kinase modulating activity using one or more of the following methods.

Method 1. A biochemical assay is performed employing commercially-obtained kinase, commercially-obtained substrate, commercially-obtained kinase inhibitor (control), and semi-purified inhibitor ligand of the invention (decoy ligand). Decoy ligands are linked to an epitope tag at one end of the polypeptide for purification and/or immobilization, for example, on a microtiter plate. The tagged decoy ligand is made using an in vitro transcription/translation system such as a reticulocyte lysate system well known in the art. A vector polynucleotide comprising a promotor, such as T7 and/or T3 and/or SP6 promotor, a decoy ligand coding sequence, and an epitope tag coding sequence is employed to synthesize the tagged decoy ligand in an in vitro transcription/translation system. In vitro transcription/translation protocols are disclosed in reference manuals such as: Current Protocols in Molecular Biology (eds. Ausubel et al., Wiley, 2004 edition.) and Molecular Cloning: A Laboratory Manual (Sambrook and Russell (Cold Spring Harbor Laboratory Press, 2001, third edition). Immunoreagent-containing methods such as

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western blots, elisas, and immunoprecipitations are performed as described in: Using Antibodies: A Laboratory Manual (Harlow and Lane Cold Spring Harbor Laboratory Press, 1999).

Specifically, tagged decoy ligand synthesized using an in vitro transcription/translation system is semi-purified and added to a microtiter plate containing kinase enzyme and substrate immobilized by an anti-substrate specific antibody. Microtiter plates are rinsed to substantially remove non-immobilized components. Kinase activity is a direct measure of the phosphorylation of substrate by kinase employing a phospho-substrate specific secondary antibody conjugated to horseradish peroxidase (HRP) followed by the addition of 3,3',5,5'-tetramethylbenzidine (TMB) substrate solution. The catalysis of TMB by HRP results in a blue color that changes to yellow upon addition of phosphoric or sulfuric acid with a maximum absorbance at 450 nm. The Control experiments include absence of kinase enzyme, and/or absence of decoy ligand, and/or presence/absence of known kinase inhibitors. A known kinase inhibitor useful in the assay is staurosporine.

Method 2. A similar assay is performed employing the same reagents as above but the substrate is biotinylated and immobilized by binding to a streptavidin-coated plate.

Method 3. A biochemical assay is performed employing commercially-obtained kinase, commercially-obtained substrate, commercially-obtained kinase inhibitor (control), and semi-purified inhibitor ligand of the invention (decoy ligand) in a microtiter plate. A luminescent-based detection system, such as Promega's Kinase-Glo, is then added to inversely measure kinase activity.

Specifically, tagged decoy ligand synthesized using an in vitro transcription/translation system is semi-purified and added to a microtiter plate containing kinase enzyme and substrate. After the kinase assay is performed, luciferase and luciferin are added to the reaction. Luciferase utilizes any remaining ATP not used by the kinase to catalyze luciferin. The luciferase reaction results in the production of light which is inversely related to kinase activity. Control experiments include absence of kinase enzyme, and/or absence of decoy ligand, and/or presence/absence of known kinase inhibitors. A known kinase inhibitor useful in the assay is staurosporine.

Method 4. A similar cell-based assay is performed employing same reagents as above, but synthesizing the decoy ligand in a mammalian cell system instead of an in vitro transcription/translation system. Decoy ligands are linked to an epitope tag at one end of the polypeptide for immobilization and/or for purification and/or for identification in a western blot. Optionally, tagged decoy ligands are also linked to a cellular localization signal for phenotypic comparison of pan-cellular and localized kinase modulation. A vector polynucleotide comprising a constitutive promotor, such as the CMV promotor, a decoy ligand coding sequence, an epitope tag coding sequence, and optionally a localization signal coding sequence is employed to express the decoy ligand in cells. Transfection and expression protocols are disclosed in reference manuals such as: Current Protocols in Molecular Biology (eds. Ausubel et al., Wiley, 2004 edition.) and Molecular Cloning: A Laboratory Manual (Sambrook and Russell (Cold Spring Harbor Laboratory Press, 2001, third edition). Western Blots and immunoreagent-containing methods are performed as described in: Using Antibodies: A Laboratory Manual (Harlow and Lane Cold Spring Harbor Laboratory Press, 1999).

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EXAMPLES

Example 1

A polypeptide comprising a heteropolyligand, an endoplasmic reticulum cellular localization signal, and a His epitope is synthesized. Examples of such polypeptides are generically represented by FIGS. 8A, 8B, 8D, 8E and 8F. The polypeptide is synthesized on an automated peptide synthesizer or is recombinantly expressed and purified. Purified polypeptide is solubilized in media and added to cells. The polypeptide is endocytosed by the cells, and transported to the endoplasmic reticulum. Verification is performed by immunohistochemical staining using an anti-His6 antibody.

Example 2

A transgene is constructed using a human cytomegalovirus (CMV) promoter to direct expression of a fusion protein comprising SEQ ID NO:96, SEQ ID NO:99, SEQ ID NO:89, wherein Xaa is alanine (POLYLIGAND), green fluorescent protein (REPORTER), and a plasma membrane localization signal (LOCALIZATION SIGNAL). Such a transgene is generically represented by FIG. 9C. The transgene is transfected into cells for transient expression. Verification of expression and location is performed by visualization of green fluorescent protein (GFP) by confocal microscopy.

Example 3

A transgene construct is built to produce a protein product with expression driven by a tissue-specific promoter. The transgene comprises a synthetic gene expression unit engineered to encode three domains. Each of these three domains is synthesized as a pair of complimentary polynucleotides that are annealed in solution, ligated and inserted into a vector. Starting at the amino-terminus, the three domains in the expression unit are nucleotide sequences that encode an ERK ligand, a FLAG™ epitope, and a nuclear localization signal. The ERK ligand is a monomeric ligand, homopolymeric ligand or heteropolymeric ligand as described herein. Nucleotide sequences encoding a FLAG™ epitope are placed downstream of nucleotide sequences encoding the ERK ligand. Finally, nucleotide sequences encoding the localization signal are placed downstream of those encoding the FLAG™ epitope. The assembled gene expression unit is subsequently subcloned into an expression vector, such as that shown in FIG. 10A, and used to transiently transfect cells. Verification is performed by immunohistochemical staining using an anti-FLAG™ antibody.

Example 4

Modulation of ERK cellular function by subcellularly localized ERK polyligand is illustrated. A transgene construct containing nucleic acids that encode a polyligand fusion protein, epitope, and endoplasmic reticulum localization signal is made. The expression unit contains nucleotides that encode SEQ ID NO:1 (POLYLIGAND), a c-Myc epitope (EPITOPE), and an endoplasmic reticulum localization signal (LOCALIZATION SIGNAL). This expression unit is subsequently subcloned into a vector between a EF1alpha promoter and an SV40 polyadenylation signal (depicted in FIG. 12). The completed transgene-containing expression vector is then used to transfect cells. Inhibition of ERK activ-

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ity is demonstrated by measuring phosphorylation of endogenous substrates against controls (see FIG. 14).

Example 5

Ligand function and localization is demonstrated in vivo by making a transgene construct used to generate mice expressing a ligand fusion protein targeted to the endoplasmic reticulum. The transgene construct is shown generically in FIG. 10B. The expression unit contains nucleotides that encode a tetramer of SEQ ID NO:65, a hemagglutinin epitope, and a nuclear localization signal. This expression unit is subsequently subcloned into a vector between nucleotide sequences including an inducible promoter and an SV40 polyadenylation signal. The completed transgene is then injected into pronuclei of fertilized mouse oocytes. The resultant pups are screened for the presence of the transgene by PCR. Transgenic founder mice are bred with wild-type mice. Heterozygous transgenic animals from at least the third generation are used for the following tests, with their non-transgenic littermates serving as controls.

Test 1: Southern blotting analysis is performed to determine the copy number. Southern blots are hybridized with a radio-labeled probe generated from a fragment of the transgene. The probe detects bands containing DNA from transgenic mice, but does not detect bands containing DNA from non-transgenic mice. Intensities of the transgenic mice bands are measured and compared with the transgene plasmid control bands to estimate copy number. This demonstrates that mice in Example 5 harbor the transgene in their genomes.

Test 2: Tissue homogenates are prepared for Western blot analysis. This experiment demonstrates the transgene is expressed in tissues of transgenic mice because hemagglutinin epitope is detected in transgenic homogenates but not in non-transgenic homogenates.

Test 3: Function is assessed by phenotypic observation or analysis against controls.

These examples demonstrate delivery of ligands to a localized region of a cell for therapeutic or experimental purposes. The purified polypeptide ligands can be formulated for oral or parenteral administration, topical administration, or in tablet, capsule, or liquid form, intranasal or inhaled aerosol, subcutaneous, intramuscular, intraperitoneal, or other injection; intravenous instillation; or any other routes of administration. Furthermore, the nucleotide sequences encoding the ligands permit incorporation into a vector designed to deliver and express a gene product in a cell. Such vectors include plasmids, cosmids, artificial chromosomes, and modified viruses. Delivery to eukaryotic cells can be accomplished in vivo or ex vivo. Ex vivo delivery methods include isolation of the intended recipient's cells or donor cells and delivery of the vector to those cells, followed by treatment of the recipient with the cells.

55 Results

Results show that the ERK polyligands of the invention (decoys) localized to the appropriate subcellular compartments and inhibited ERK activity at those locations. Localized inhibition caused distinct functional changes in the treated cells, including inhibition of oncogene-induced cell proliferation and transformation. Furthermore, depending on the source of the activation signal for the ERK pathway, the specific subcellular site of inhibition (endoplasmic reticulum or plasma membrane) had a differentiating effect on transformation phenotype of the cells. In contrast, inhibition of ERK by siRNA or a small molecule inhibitor did not reveal this functional difference.

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Fluorescence microscopy of the ligand of SEQ ID NO:1 is shown localized to the nucleus (FIG. 16), cytoplasm (FIG. 17), and endoplasmic reticulum (FIG. 13A). The localized ERK ligands were detected by immunostaining for the c-myc epitope tag. FIG. 14 shows ERK activity localized to specific compartments with localized Ras overexpression and SEQ ID NO:1 expressed pancellularly (lanes 8-9) or targeted to the endoplasmic reticulum (lanes 5-7) or plasma membrane (lanes 2-4). The result was location-selective inhibition of ERK activity at the endoplasmic reticulum as measured by phosphorylation of the ERK substrate myelin basic protein (MBP).

Additionally, experiments where inhibition of ERK signaling using ERK ligands of the invention was compared to siRNAs and a small molecule inhibitor. The commercial siRNAs were designed for target specificity to either the ERK1 (sc-29307) or ERK2 (sc-35335) isoforms (Santa Cruz Biotechnology, Inc.). The small molecule inhibitor, UO126 (1,4-diamino-2,3-dicyano-1,4-bis(2-aminophenylthio)butadiene), inhibits ERK signaling through its upstream effector, MEK, and ERK is the only known substrate for MEK. Assays performed were phenotypic assays. The effects of inhibiting ERK activity were measured by looking at functional properties of the cells associated with the MAPK signaling pathway, such as, cell proliferation and transformation. The MAPK signaling cascade in these experiments is initiated by transfection of the cells with a vector containing a constitutively active proto-oncogene, either H-RasV12 or v-Src, which eventually causes the cells to acquire enhanced growth rate (colony formation) and cell transformation rate (foci formation). Inhibition of ERK activity in this cascade will result in reduced rates of proliferation or transformation as measured by numbers of G418-resistant colonies or foci.

Data for colony formation inhibition with the various treatments is presented in FIG. 18. UO126 is very effective at inhibiting the pathway due to its high potency for MEK (~70 nM) and its stability. Furthermore, the siRNAs targeted against ERK1 or ERK2 show isoform specificity as to the effects on proliferation. This is consistent with a recent report that showed interplay between ERK1 and ERK2 in regulating Ras-mediated signaling, wherein ERK2 has a positive role in controlling cell proliferation and ERK1 can affect signal output by counteracting ERK2 activity (Vantaggiato et al. 2006 J. of Biol. 5:14). The two ERK ligands (SEQ ID NO:1 and SEQ ID NO:5, both fused to c-Myc and FLAG tags) used in this experiment are not targeted to a specific subcellular location but are expressed throughout the cell under the control of a constitutive promoter. The ERK ligands, as described herein, are designed with multiple domains (usually mutated substrates) believed capable of competing with the normal endogenous ERK substrates. Thus, unlike siRNAs, which can have RNA sequence specificity for each of the two isoforms of ERK, the ERK decoy ligands may bind to both ERK1 and ERK2 proteins, which may result in only partial inhibition of

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cell proliferation. Possible reasons for partial inhibition may include a titration effect whereby some of the decoy ligand is “trapped” by ERK1 and unavailable to inhibit ERK2. Partial inhibition may also be due to the inhibition of the ERK1, possibly antagonizing or mitigating the inhibitory effects on ERK2.

Based on the similar effectiveness of SEQ ID NO:1 and SEQ ID NO:5 in inhibiting Ras-mediated cell proliferation, a similar experiment was conducted with SEQ ID NO:1 localized to the nucleus (NLS), the cytoplasm (NXP, nuclear exclusion), the endoplasmic reticulum (ER), and the plasma membrane (PLA). In all cases, location-specific SEQ ID NO:1 causes some inhibition of cell proliferation, with the greatest degree of inhibition arising when the decoy is localized to the plasma membrane (FIG. 19). ER-localized inhibition was also significant, consistent with the results previously reported using dominant negative location-targeted Ras inhibitors (Matallanas et al. (2006) Mol. Cell. Biol. 26: 100-116). SEQ ID NO:1 targeted to the nucleus and cytoplasm gives slight inhibition of proliferation.

Next, the effect of ERK inhibition on cell transformation was investigated using two means of initiating signaling cascades that lead to this biological property (FIG. 20). The first method is the constitutively active Ras mutant used herein above. The second is a constitutively active nonreceptor tyrosine kinase v-Src mutant (pp60v-src) that also leads to cell transformation, potentially by multiple signaling pathways including the Ras-Raf-MEK-ERK pathway. As shown in FIG. 20, the pancellular decoys (SEQ ID NO:1 and SEQ ID NO:5), ERK2 siRNA, and localized decoy (SEQ ID NO:1 fused to localization signals indicated) all inhibited cell transformation. Treatment of H-RasV12 transformed cells with ER-localized and PLA-localized SEQ ID NO:1 inhibited cell transformation rates by ~50%, similar to results obtained with the pancellularly expressed SEQ ID NO:1 and SEQ ID NO:5. However, when transformation was initiated with v-Src, there was a difference in the inhibition specificity arising from use of SEQ ID NO:1 localized to the ER and PLA. The ER-localized SEQ ID NO:1 caused little to no inhibition relative to the untreated control, while the PLA-localized SEQ ID NO:1 caused ~60% decrease in transformation. That is, ER-localized SEQ ID NO:1 has a significant effect on transformation induced by H-RasV12 but little to no effect when transformation is induced by v-Src. In contrast, inhibition of ERK by siRNA was identical for both the H-Ras and v-Src pathways. Thus, siRNA does not differentiate the effects on transformation induced by distinct oncogenes H-Ras and v-Src.

Disclosed are ligands and polyligands that modulate ERK activity and methods of making and using these ligands. The ligands and polyligands are synthesized chemically or recombinantly and are utilized as research tools or as therapeutics. The invention includes linking the ligands and polyligands to cellular localization signals for subcellular therapeutics.

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306

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Ala	Pro	Pro	Pro	Ser	Gln	Gly	Lys	Gly	Gly	Gly	Thr	Leu	Ser	Pro		
		50														60
Ile	Ala	Pro	Arg	Ala	Pro	Ala	Lys	Leu	Ser	Phe	Gln	Phe	Pro	Ser	Ser	
		65														80
Ala	Gly	Pro	Gly	Ala	Glu	Phe	Leu	Lys	Pro	Ile	Glu	Ser	Ser	Ile	Leu	
		85														95
Ala	Gln	Arg	Arg	Val	Arg	Lys	Leu	Pro	Ser	Thr	Ala	Gly	Lys			
		100														110
Arg	Glu	Leu	Val	Glu	Pro	Leu	Ala	Pro	Ser	Gly	Glu	Ala	Pro	Asn	Gln	
		115														125
Ala	Leu	Leu	Arg	Ala	Ala	Gly	Gly	Tyr	Ser	Pro	Thr	Ala	Pro	Thr	Tyr	
		130														140
Ser	Pro	Thr	Ala	Pro	Lys	Lys	Gly	Ala	Ala	Thr	Pro	Thr	Ala			
		145														160
Ala	His	Ser	Gly	Ser	His	Leu	Phe	Gly	Phe	Pro						
		165														170

<210> SEQ ID NO 6
<211> LENGTH: 513
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polyligand

<400> SEQUENCE: 6

ccccccctga	tggccccc	cttctacccc	cagaaggcga	ggaagcctag	ggacctggag	60
ctgccccctgg	ccgcccgcgc	caagcaggcc	gaggccgtga	ccgccccccag	gggcgcgtggc	120
gccaagaaca	tcgtgacccc	cagggccccc	ccccccagcc	agggcaaggg	cgccggccgc	180
accctgagcc	ccatcgcccc	cagggccccc	gccaagctga	gcttccagg	ccccagcagc	240
gttgcccccgg	gcgcgcgagtt	cctgaagccc	atcgagagca	gcatcctggc	ccagaggagg	300
gtgaggaagc	tgcccagcac	cgctggcgct	ggcaagagg	agctggtgga	gccccctggcc	360
cccaagggcg	aggcccccaa	ccaggccctg	ctgagggccg	ctggcgcccta	cagccccacc	420
gccccccacct	acagccccac	cgcccccaag	aagaaggccg	gogccgcac	ccccaccgcc	480
gccccacagcg	gcagccac	gttcggcttc	ccc			513

<210> SEQ ID NO 7
<211> LENGTH: 540
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: Synthetic polyligand

<400> SEQUENCE: 7

gcccggcccc	ccctgatggc	cccccccttc	taccccccaga	agggcaggaa	gcctaggac	60
ctggagctgc	ccctggccgc	cgcgcacaag	caggccgagg	ccgtgaccgc	ccccagggc	120
gttggcgcca	agaacatcg	gaccccccagg	gccccccccc	ccagccagg	caagggccgc	180
ggcggcaccc	tgageccccat	cgccccagg	gcccccgcca	agctgagctt	ccagttcccc	240
agcagcgctg	gccccggcgc	cgagttctg	aagccatcg	agagcagcat	cctggccag	300
aggagggtga	ggaagctgcc	cagcacccgt	ggcgctggca	agagggagct	ggtgagcc	360
ctggccccca	gcggcgaggc	ccccaaaccag	gcccctgtga	gggcccgtgg	cggtcacagc	420
cccacccgccc	ccacctacag	ccccacccgcc	cccaagaaga	agggcggcgc	cgccacccccc	480
accggccgccc	acagcggcag	ccacctgttc	ggttcccc	ccggggggcgg	aggcatcgat	540

<210> SEQ ID NO 8

<211> LENGTH: 540

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic polyligand

<400> SEQUENCE: 8

gtagcccccc	ctttgatggc	tccggccgttc	taccctcaga	agggtcgaa	accaaggat	60
tcgaaactgc	ccctcgctgc	cggcgcaaag	caggccgaa	ctgtgaccgc	acctagaggg	120
gcgggggtgcga	agaacatagt	aactccacgg	gcacccctcg	catcccagg	gaagggcggt	180
ggcggggacgc	tgagtccaat	cgccccagg	gctcctgcca	agttgagttt	ccagttcccc	240
tcaagcgccg	ggcctggagc	tgagttctc	aagccatag	agtccagtat	cctcgctcaa	300
cgacgggtga	aaaaactgcc	ctccacggca	ggggcaggt	agagagaact	ggttgagcct	360
ctggcccccta	gcggcgaagc	gccgaacca	gcattgttc	gcgtgcgg	ggggatttca	420
ccccacagcgc	ctacctattc	tcccacagcc	cctaagaaga	agggcggagc	ggctacacct	480
acggccgctc	atacgggatc	tcacctgttt	ggtttcccc	ccggggggagg	cggaatcgat	540

<210> SEQ ID NO 9

<211> LENGTH: 418

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (412)..(412)

<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 9

Met	Gly	Asp	Lys	Gly	Thr	Arg	Val	Phe	Lys	Lys	Ala	Ser	Pro	Asn	Gly
1							5		10						15

Lys	Leu	Thr	Val	Tyr	Leu	Gly	Lys	Arg	Asp	Phe	Val	Asp	His	Ile	Asp
			20				25						30		

Leu	Val	Asp	Pro	Val	Asp	Gly	Val	Val	Leu	Val	Asp	Pro	Glu	Tyr	Leu
			35				40						45		

Lys	Glu	Arg	Arg	Val	Tyr	Val	Thr	Leu	Thr	Cys	Ala	Phe	Arg	Tyr	Gly
	50						55			60					

Arg	Glu	Asp	Leu	Asp	Val	Leu	Gly	Leu	Thr	Phe	Arg	Lys	Asp	Leu	Phe
65							70			75					80

Val	Ala	Asn	Val	Gln	Ser	Phe	Pro	Pro	Ala	Pro	Glu	Asp	Lys	Pro	
							85			90			95		

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Leu Thr Arg Leu Gln Glu Arg Leu Ile Lys Lys Leu Gly Glu His Ala
 100 105 110
 Tyr Pro Phe Thr Phe Glu Ile Pro Pro Asn Leu Pro Cys Ser Val Thr
 115 120 125
 Leu Gln Pro Gly Pro Glu Asp Thr Gly Lys Ala Cys Gly Val Asp Tyr
 130 135 140
 Glu Val Lys Ala Phe Cys Ala Glu Asn Leu Glu Glu Lys Ile His Lys
 145 150 155 160
 Arg Asn Ser Val Arg Leu Val Ile Arg Lys Val Gln Tyr Ala Pro Glu
 165 170 175
 Arg Pro Gly Pro Gln Pro Thr Ala Glu Thr Thr Arg Gln Phe Leu Met
 180 185 190
 Ser Asp Lys Pro Leu His Leu Glu Ala Ser Leu Asp Lys Glu Ile Tyr
 195 200 205
 Tyr His Gly Glu Pro Ile Ser Val Asn Val His Val Thr Asn Asn Thr
 210 215 220
 Asn Lys Thr Val Lys Ile Lys Ile Ser Val Arg Gln Tyr Ala Asp
 225 230 235 240
 Ile Cys Leu Phe Asn Thr Ala Gln Tyr Lys Cys Pro Val Ala Met Glu
 245 250 255
 Glu Ala Asp Asp Thr Val Ala Pro Ser Ser Thr Phe Cys Lys Val Tyr
 260 265 270
 Thr Leu Thr Pro Phe Leu Ala Asn Asn Arg Glu Lys Arg Gly Leu Ala
 275 280 285
 Leu Asp Gly Lys Leu Lys His Glu Asp Thr Asn Leu Ala Ser Ser Thr
 290 295 300
 Leu Leu Arg Glu Gly Ala Asn Arg Glu Ile Leu Gly Ile Ile Val Ser
 305 310 315 320
 Tyr Lys Val Lys Val Lys Leu Val Val Ser Arg Gly Gly Leu Leu Gly
 325 330 335
 Asp Leu Ala Ser Ser Asp Val Ala Val Glu Leu Pro Phe Thr Leu Met
 340 345 350
 His Pro Lys Pro Lys Glu Glu Pro Pro His Arg Glu Val Pro Glu Asn
 355 360 365
 Glu Thr Pro Val Asp Thr Asn Leu Ile Glu Leu Asp Thr Asn Asp Asp
 370 375 380
 Asp Ile Val Phe Glu Asp Phe Ala Arg Gln Arg Leu Lys Gly Met Lys
 385 390 395 400
 Asp Asp Lys Glu Glu Glu Asp Gly Thr Gly Xaa Pro Gln Leu Asn
 405 410 415
 Asn Arg

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<210> SEQ_ID NO 10
<211> LENGTH: 505
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (90)..(90)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 10

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Met Lys Phe Lys Leu His Val Asn Ser Ala Arg Gln Tyr Lys Asp Leu
 1 5 10 15

Trp Asn Met Ser Asp Asp Lys Pro Phe Leu Cys Thr Ala Pro Gly Cys

-continued

20	25	30
Gly Gln Arg Phe Thr Asn Glu Asp His Leu Ala Val His Lys His Lys		
35	40	45
His Glu Met Thr Leu Lys Phe Gly Pro Ala Arg Asn Asp Ser Val Ile		
50	55	60
Val Ala Asp Gln Thr Pro Thr Pro Thr Arg Phe Leu Lys Asn Cys Glu		
65	70	75
Glu Val Gly Leu Phe Asn Glu Leu Ala Xaa Pro Phe Glu Asn Glu Phe		
85	90	95
Lys Lys Ala Ser Glu Asp Asp Ile Lys Lys Met Pro Leu Asp Leu Ser		
100	105	110
Pro Leu Ala Thr Pro Ile Ile Arg Ser Lys Ile Glu Glu Pro Ser Val		
115	120	125
Val Glu Thr Thr His Gln Asp Ser Pro Leu Pro His Pro Glu Ser Thr		
130	135	140
Thr Ser Asp Glu Lys Glu Val Pro Leu Ala Gln Thr Ala Gln Pro Thr		
145	150	155
160		
Ser Ala Ile Val Arg Pro Ala Ser Leu Gln Val Pro Asn Val Leu Leu		
165	170	175
Thr Ser Ser Asp Ser Ser Val Ile Ile Gln Gln Ala Val Pro Ser Pro		
180	185	190
Thr Ser Ser Thr Val Ile Thr Gln Ala Pro Ser Ser Asn Arg Pro Ile		
195	200	205
Val Pro Val Pro Gly Pro Phe Pro Leu Leu His Leu Pro Asn Gly		
210	215	220
Gln Thr Met Pro Val Ala Ile Pro Ala Ser Ile Thr Ser Ser Asn Val		
225	230	235
240		
His Val Pro Ala Ala Val Pro Leu Val Arg Pro Val Thr Met Val Pro		
245	250	255
Ser Val Pro Gly Ile Pro Gly Pro Ser Ser Pro Gln Pro Val Gln Ser		
260	265	270
Glu Ala Lys Met Arg Leu Lys Ala Ala Leu Thr Gln Gln His Pro Pro		
275	280	285
Val Thr Asn Gly Asp Thr Val Lys Gly His Gly Ser Gly Leu Val Arg		
290	295	300
Thr Gln Ser Glu Glu Ser Arg Pro Gln Ser Leu Gln Gln Pro Ala Thr		
305	310	315
320		
Ser Thr Thr Glu Thr Pro Ala Ser Pro Ala His Thr Thr Pro Gln Thr		
325	330	335
Gln Ser Thr Ser Gly Arg Arg Arg Ala Ala Asn Glu Asp Pro Asp		
340	345	350
Glu Lys Arg Arg Lys Phe Leu Glu Arg Asn Arg Ala Ala Ala Ser Arg		
355	360	365
Cys Arg Gln Lys Arg Lys Val Trp Val Gln Ser Leu Glu Lys Lys Ala		
370	375	380
Glu Asp Leu Ser Ser Leu Asn Gly Gln Leu Gln Ser Glu Val Thr Leu		
385	390	395
400		
Leu Arg Asn Glu Val Ala Gln Leu Lys Gln Leu Leu Leu Ala His Lys		
405	410	415
Asp Cys Pro Val Thr Ala Met Gln Lys Lys Ser Gly Tyr His Thr Ala		
420	425	430
Asp Lys Asp Asp Ser Ser Glu Asp Ile Ser Val Pro Ser Ser Pro His		
435	440	445

-continued

Thr Glu Ala Ile Gln His Ser Ser Val Thr Ser Asn Gly Val Ser
 450 455 460

Ser Thr Ser Lys Ala Glu Ala Val Ala Thr Ser Val Leu Thr Gln Met
 465 470 475 480

Ala Asp Gln Ser Thr Glu Pro Ala Leu Ser Gln Ile Val Met Ala Pro
 485 490 495

Ser Ser Gln Ser Gln Pro Ser Gly Ser
 500 505

<210> SEQ ID NO 11

<211> LENGTH: 793

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (789)..(789)

<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 11

Met Asp Asp Phe Glu Arg Arg Arg Glu Leu Arg Arg Gln Lys Arg Glu
 1 5 10 15

Glu Met Arg Leu Glu Ala Glu Arg Ile Ala Tyr Gln Arg Asn Asp Asp
 20 25 30

Asp Glu Glu Glu Ala Ala Arg Glu Arg Arg Arg Ala Arg Gln Glu
 35 40 45

Arg Leu Arg Gln Lys Gln Glu Glu Ser Leu Gly Gln Val Thr Asp
 50 55 60

Gln Val Glu Val Asn Ala Gln Asn Ser Val Pro Asp Glu Ala Lys
 65 70 75 80

Thr Thr Thr Asn Thr Gln Val Glu Gly Asp Asp Glu Ala Ala Phe
 85 90 95

Leu Glu Arg Leu Ala Arg Arg Glu Glu Arg Arg Gln Lys Arg Leu Gln
 100 105 110

Glu Ala Leu Glu Arg Gln Lys Glu Phe Asp Pro Thr Ile Thr Asp Ala
 115 120 125

Ser Leu Ser Leu Pro Ser Arg Arg Met Gln Asn Asp Thr Ala Glu Asn
 130 135 140

Glu Thr Thr Glu Lys Glu Glu Lys Ser Glu Ser Arg Gln Glu Arg Tyr
 145 150 155 160

Glu Ile Glu Glu Thr Glu Thr Val Thr Lys Ser Tyr Gln Lys Asn Asp
 165 170 175

Trp Arg Asp Ala Glu Glu Asn Lys Lys Glu Asp Lys Glu Lys Glu Glu
 180 185 190

Glu Glu Glu Lys Pro Lys Arg Gly Ser Ile Gly Glu Asn Gln Val
 195 200 205

Glu Val Met Val Glu Glu Lys Thr Thr Glu Ser Gln Glu Glu Thr Val
 210 215 220

Val Met Ser Leu Lys Asn Gly Gln Ile Ser Ser Glu Glu Pro Lys Gln
 225 230 235 240

Glu Glu Glu Arg Glu Gln Gly Ser Asp Glu Ile Ser His His Glu Lys
 245 250 255

Met Glu Glu Glu Asp Lys Glu Arg Ala Glu Ala Glu Arg Ala Arg Leu
 260 265 270

Glu Ala Glu Glu Arg Glu Arg Ile Lys Ala Glu Gln Asp Lys Lys Ile
 275 280 285

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Ala Asp Glu Arg Ala Arg Ile Glu Ala Glu Glu Lys Ala Ala Ala Gln
 290 295 300

Glu Arg Glu Arg Arg Glu Ala Glu Glu Arg Glu Arg Met Arg Glu Glu
 305 310 315 320

Glu Lys Arg Ala Ala Glu Glu Arg Gln Arg Ile Lys Glu Glu Glu Lys
 325 330 335

Arg Ala Ala Glu Glu Arg Gln Arg Ile Lys Glu Glu Glu Lys Arg Ala
 340 345 350

Ala Glu Glu Arg Gln Arg Ile Lys Glu Glu Glu Lys Arg Ala Ala Glu
 355 360 365

Glu Arg Gln Arg Ala Arg Ile Lys Glu Glu Glu Lys Ala Lys Val Glu
 370 375 380

Glu Gln Lys Arg Asn Lys Gln Leu Glu Glu Lys Lys His Ala Met Gln
 385 390 395 400

Glu Thr Lys Ile Lys Gly Glu Lys Val Glu Gln Lys Ile Glu Gly Lys
 405 410 415

Trp Val Asn Glu Lys Lys Ala Gln Glu Asp Lys Leu Gln Thr Ala Val
 420 425 430

Leu Lys Lys Gln Gly Glu Glu Lys Gly Thr Lys Val Gln Ala Lys Arg
 435 440 445

Glu Lys Leu Gln Glu Asp Lys Pro Thr Phe Lys Lys Glu Glu Ile Lys
 450 455 460

Asp Glu Lys Ile Lys Lys Asp Lys Glu Pro Lys Glu Glu Val Lys Ser
 465 470 475 480

Phe Met Asp Arg Lys Lys Gly Phe Thr Glu Val Lys Ser Gln Asn Gly
 485 490 495

Glu Phe Met Thr His Lys Leu Lys His Thr Glu Asn Thr Phe Ser Arg
 500 505 510

Pro Gly Gly Arg Ala Ser Val Asp Thr Lys Glu Ala Glu Gly Ala Pro
 515 520 525

Gln Val Glu Ala Gly Lys Arg Leu Glu Glu Leu Arg Arg Arg Arg Gly
 530 535 540

Glu Thr Glu Ser Glu Glu Phe Glu Lys Leu Lys Gln Lys Gln Glu
 545 550 555 560

Ala Ala Leu Glu Leu Glu Leu Lys Lys Lys Arg Glu Arg Arg Arg
 565 570 575

Lys Val Leu Glu Glu Glu Gln Arg Arg Lys Gln Glu Glu Ala Asp
 580 585 590

Arg Lys Leu Arg Glu Glu Glu Lys Arg Arg Leu Lys Glu Glu Ile
 595 600 605

Glu Arg Arg Arg Ala Glu Ala Ala Glu Lys Arg Gln Lys Met Pro Glu
 610 615 620

Asp Gly Leu Ser Asp Asp Lys Lys Pro Phe Lys Cys Phe Thr Pro Lys
 625 630 635 640

Gly Ser Ser Leu Lys Ile Glu Glu Arg Ala Glu Phe Leu Asn Lys Ser
 645 650 655

Val Gln Lys Ser Ser Gly Val Lys Ser Thr His Gln Ala Ala Ile Val
 660 665 670

Ser Lys Ile Asp Ser Arg Leu Glu Gln Tyr Thr Ser Ala Ile Glu Gly
 675 680 685

Thr Lys Ser Ala Lys Pro Thr Lys Pro Ala Ala Ser Asp Leu Pro Val
 690 695 700

Pro Ala Glu Gly Val Arg Asn Ile Lys Ser Met Trp Glu Lys Gly Asn

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705	710	715	720
Val Phe Ser Ser Pro Thr Ala Ala Gly Thr Pro Asn Lys Glu Thr Ala			
725	730	735	
Gly Leu Lys Val Gly Val Ser Ser Arg Ile Asn Glu Trp Leu Thr Lys			
740	745	750	
Thr Pro Asp Gly Asn Lys Ser Pro Ala Pro Lys Pro Ser Asp Leu Arg			
755	760	765	
Pro Gly Asp Val Ser Ser Lys Arg Asn Leu Trp Glu Lys Gln Ser Val			
770	775	780	
Asp Lys Val Thr Xaa Pro Thr Lys Val			
785	790		

<210> SEQ_ID NO 12
<211> LENGTH: 473
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (216)..(216)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 12

Met Ser Thr Glu Leu Phe Ser Ser Thr Arg Glu Glu Gly Ser Ser Gly			
1	5	10	15

Ser Gly Pro Ser Phe Arg Ser Asn Gln Arg Lys Met Leu Asn Leu Leu		
20	25	30

Leu Glu Arg Asp Thr Ser Phe Thr Val Cys Pro Asp Val Pro Arg Thr		
35	40	45

Pro Val Gly Lys Phe Leu Gly Asp Ser Ala Asn Leu Ser Ile Leu Ser		
50	55	60

Gly Gly Thr Pro Lys Cys Cys Leu Asp Leu Ser Asn Leu Ser Ser Gly			
65	70	75	80

Glu Ile Thr Ala Thr Gln Leu Thr Thr Ser Ala Asp Leu Asp Glu Thr		
85	90	95

Gly His Leu Asp Ser Ser Gly Leu Gln Glu Val His Leu Ala Gly Met		
100	105	110

Asn His Asp Gln His Leu Met Lys Cys Ser Pro Ala Gln Leu Cys		
115	120	125

Ser Thr Pro Asn Gly Leu Asp Arg Gly His Arg Lys Arg Asp Ala Met		
130	135	140

Cys Ser Ser Ser Ala Asn Lys Glu Asn Asp Asn Gly Asn Leu Val Asp			
145	150	155	160

Ser Glu Met Lys Tyr Leu Gly Ser Pro Ile Thr Thr Val Pro Lys Leu		
165	170	175

Asp Lys Asn Pro Asn Leu Gly Glu Asp Gln Ala Glu Glu Ile Ser Asp		
180	185	190

Glu Leu Met Glu Phe Ser Leu Lys Asp Gln Glu Ala Lys Val Ser Arg		
195	200	205

Ser Gly Leu Tyr Arg Ser Pro Xaa Met Pro Glu Asn Leu Asn Arg Pro		
210	215	220

Arg Leu Lys Gln Val Glu Lys Phe Lys Asp Asn Thr Ile Pro Asp Lys			
225	230	235	240

Val Lys Lys Lys Tyr Phe Ser Gly Gln Gly Lys Leu Arg Lys Gly Leu		
245	250	255

Cys Leu Lys Lys Thr Val Ser Leu Cys Asp Ile Thr Ile Thr Gln Met		
260	265	270

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Leu Glu Glu Asp Ser Asn Gln Gly His Leu Ile Gly Asp Phe Ser Lys
 275 280 285
 Val Cys Ala Leu Pro Thr Val Ser Gly Lys His Gln Asp Leu Lys Tyr
 290 295 300
 Val Asn Pro Glu Thr Val Ala Ala Leu Leu Ser Gly Lys Phe Gln Gly
 305 310 315 320
 Leu Ile Glu Lys Phe Tyr Val Ile Asp Cys Arg Tyr Pro Tyr Glu Tyr
 325 330 335
 Leu Gly Gly His Ile Gln Gly Ala Leu Asn Leu Tyr Ser Gln Glu Glu
 340 345 350
 Leu Phe Asn Phe Phe Leu Lys Lys Pro Ile Val Pro Leu Asp Thr Gln
 355 360 365
 Lys Arg Ile Ile Ile Val Phe His Cys Glu Phe Ser Ser Glu Arg Gly
 370 375 380
 Pro Arg Met Cys Arg Cys Leu Arg Glu Glu Asp Arg Ser Leu Asn Gln
 385 390 395 400
 Tyr Pro Ala Leu Tyr Tyr Pro Glu Leu Tyr Ile Leu Lys Gly Gly Tyr
 405 410 415
 Arg Asp Phe Phe Pro Glu Tyr Met Glu Leu Cys Glu Pro Gln Ser Tyr
 420 425 430
 Cys Pro Met His His Gln Asp His Lys Thr Glu Leu Leu Arg Cys Arg
 435 440 445
 Ser Gln Ser Lys Val Gln Glu Gly Glu Arg Gln Leu Arg Glu Gln Ile
 450 455 460
 Ala Leu Leu Val Lys Asp Met Ser Pro
 465 470

<210> SEQ ID NO 13
 <211> LENGTH: 126
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <221> NAME/KEY: misc_feature
 <222> LOCATION: (23)..(23)
 <223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 13

Met	Ser	Tyr	Lys	Pro	Ile	Ala	Pro	Ala	Pro	Ser	Ser	Thr	Pro	Gly	Ser
1					5				10				15		

Ser Thr Pro Gly Pro Gly Xaa Pro Val Pro Thr Gly Ser Val Pro Ser
 20 25 30

Pro	Ser	Gly	Ser	Val	Pro	Gly	Ala	Gly	Ala	Pro	Phe	Arg	Pro	Leu	Phe
35					40					45					

Asn Asp Phe Gly Pro Pro Ser Met Gly Tyr Val Gln Ala Met Lys Pro
 50 55 60

Pro	Gly	Ala	Gln	Gly	Ser	Gln	Ser	Thr	Tyr	Thr	Asp	Leu	Leu	Ser	Val
65					70			75			80				

Ile Glu Glu Met Gly Lys Glu Ile Arg Pro Thr Tyr Ala Gly Ser Lys
 85 90 95

Ser	Ala	Met	Glu	Arg	Leu	Lys	Arg	Gly	Ile	Ile	His	Ala	Arg	Ala	Leu
100					105					110					

Val Arg Glu Cys Leu Ala Glu Thr Glu Arg Asn Ala Arg Thr
 115 120 125

<210> SEQ ID NO 14
 <211> LENGTH: 428

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (324)..(324)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (336)..(336)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (383)..(383)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (389)..(389)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (422)..(422)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 14

Met Asp Pro Ser Val Thr Leu Trp Gln Phe Leu Leu Gln Leu Leu Arg
1           5          10          15

Glu Gln Gly Asn Gly His Ile Ile Ser Trp Thr Ser Arg Asp Gly Gly
20          25          30

Glu Phe Lys Leu Val Asp Ala Glu Glu Val Ala Arg Leu Trp Gly Leu
35          40          45

Arg Lys Asn Lys Thr Asn Met Asn Tyr Asp Lys Leu Ser Arg Ala Leu
50          55          60

Arg Tyr Tyr Tyr Asp Lys Asn Ile Ile Arg Lys Val Ser Gly Gln Lys
65          70          75          80

Phe Val Tyr Lys Phe Val Ser Tyr Pro Glu Val Ala Gly Cys Ser Thr
85          90          95

Glu Asp Cys Pro Pro Gln Pro Glu Val Ser Val Thr Ser Thr Met Pro
100         105         110

Asn Val Ala Pro Ala Ala Ile His Ala Ala Pro Gly Asp Thr Val Ser
115         120         125

Gly Lys Pro Gly Thr Pro Lys Gly Ala Gly Met Ala Gly Pro Gly Gly
130         135         140

Leu Ala Arg Ser Ser Arg Asn Glu Tyr Met Arg Ser Gly Leu Tyr Ser
145         150         155         160

Thr Phe Thr Ile Gln Ser Leu Gln Pro Gln Pro Pro Pro His Pro Arg
165         170         175

Pro Ala Val Val Leu Pro Asn Ala Ala Pro Ala Gly Ala Ala Ala Pro
180         185         190

Pro Ser Gly Ser Arg Ser Thr Ser Pro Ser Pro Leu Glu Ala Cys Leu
195         200         205

Glu Ala Glu Glu Ala Gly Leu Pro Leu Gln Val Ile Leu Thr Pro Pro
210         215         220

Glu Ala Pro Asn Leu Lys Ser Glu Glu Leu Asn Val Glu Pro Gly Leu
225         230         235         240

Gly Arg Ala Leu Pro Pro Glu Val Lys Val Glu Gly Pro Lys Glu Glu
245         250         255

Leu Glu Val Ala Gly Glu Arg Gly Phe Val Pro Glu Thr Thr Lys Ala
260         265         270

Glu Pro Glu Val Pro Pro Gln Glu Gly Val Pro Ala Arg Leu Pro Ala
275         280         285

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Val Val Met Asp Thr Ala Gly Gln Ala Gly Gly His Ala Ala Ser Ser
290 295 300

Pro Glu Ile Ser Gln Pro Gln Lys Gly Arg Lys Pro Arg Asp Leu Glu
305 310 315 320

Leu Pro Leu Xaa Pro Ser Leu Leu Gly Gly Pro Gly Pro Glu Arg Xaa
325 330 335

Pro Gly Ser Gly Ser Gly Leu Gln Ala Pro Gly Pro Ala Leu
340 345 350

Thr Pro Ser Leu Leu Pro Thr His Thr Leu Thr Pro Val Leu Leu Thr
355 360 365

Pro Ser Ser Leu Pro Pro Ser Ile His Phe Trp Ser Thr Leu Xaa Pro
370 375 380

Ile Ala Pro Arg Xaa Pro Ala Lys Leu Ser Phe Gln Phe Pro Ser Ser
385 390 395 400

Gly Ser Ala Gln Val His Ile Pro Ser Ile Ser Val Asp Gly Leu Ser
405 410 415

Thr Pro Val Val Leu Xaa Pro Gly Pro Gln Lys Pro
420 425

<210> SEQ ID NO 15
<211> LENGTH: 676
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (623)..(623)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 15

Met Ser Gly Gly Asp Val Val Cys Thr Gly Trp Leu Arg Lys Ser
1 5 10 15

Pro Pro Glu Lys Lys Leu Arg Arg Tyr Ala Trp Lys Lys Arg Trp Phe
20 25 30

Ile Leu Arg Ser Gly Arg Met Ser Gly Asp Pro Asp Val Leu Glu Tyr
35 40 45

Tyr Lys Asn Asp His Ser Lys Lys Pro Leu Arg Ile Ile Asn Leu Asn
50 55 60

Phe Cys Glu Gln Val Asp Ala Gly Leu Thr Phe Asn Lys Lys Glu Leu
65 70 75 80

Gln Asp Ser Phe Val Phe Asp Ile Lys Thr Ser Glu Arg Thr Phe Tyr
85 90 95

Leu Val Ala Glu Thr Glu Glu Asp Met Asn Lys Trp Val Gln Ser Ile
100 105 110

Cys Gln Ile Cys Gly Phe Asn Gln Ala Glu Glu Ser Thr Asp Ser Leu
115 120 125

Arg Asn Val Ser Ser Ala Gly His Gly Pro Arg Ser Ser Pro Ala Glu
130 135 140

Leu Ser Ser Ser Ser Gln His Leu Leu Arg Glu Arg Lys Ser Ser Ala
145 150 155 160

Pro Ser His Ser Ser Gln Pro Thr Leu Phe Thr Phe Glu Pro Pro Val
165 170 175

Ser Asn His Met Gln Pro Thr Leu Ser Thr Ser Ala Pro Gln Glu Tyr
180 185 190

Leu Tyr Leu His Gln Cys Ile Ser Arg Arg Ala Glu Asn Ala Arg Ser
195 200 205

Ala Ser Phe Ser Gln Gly Thr Arg Ala Ser Phe Leu Met Arg Ser Asp

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210	215	220
Thr Ala Val Gln Lys Leu Ala Gln Gly Asn Gly His Cys Val Asn Gly		
225	230	235
Ile Ser Gly Gln Val His Gly Phe Tyr Ser Leu Pro Lys Pro Ser Arg		
245	250	255
His Asn Thr Glu Phe Arg Asp Ser Thr Tyr Asp Leu Pro Arg Ser Leu		
260	265	270
Ala Ser His Gly His Thr Lys Gly Ser Leu Thr Gly Ser Glu Thr Asp		
275	280	285
Asn Glu Asp Val Tyr Thr Phe Lys Thr Pro Ser Asn Thr Leu Cys Arg		
290	295	300
Glu Phe Gly Asp Leu Leu Val Asp Asn Met Asp Val Pro Ala Thr Pro		
305	310	315
Leu Ser Ala Tyr Gln Ile Pro Arg Thr Phe Thr Leu Asp Lys Asn His		
325	330	335
Asn Ala Met Thr Val Ala Thr Pro Gly Asp Ser Ala Ile Ala Pro Pro		
340	345	350
Pro Arg Pro Pro Lys Pro Ser Gln Ala Glu Thr Pro Arg Trp Gly Ser		
355	360	365
Pro Gln Gln Arg Pro Pro Ile Ser Glu Asn Ser Arg Ser Val Ala Ala		
370	375	380
Thr Ile Pro Arg Arg Asn Thr Leu Pro Ala Met Asp Asn Ser Arg Leu		
385	390	395
400		
His Arg Ala Ser Ser Cys Glu Thr Tyr Glu Tyr Pro Gln Arg Gly Gly		
405	410	415
Glu Ser Ala Gly Arg Ser Ala Glu Ser Met Ser Asp Gly Val Gly Ser		
420	425	430
Phe Leu Pro Gly Lys Met Ile Val Gly Arg Ser Asp Ser Thr Asn Ser		
435	440	445
Glu Asp Asn Tyr Val Pro Met Asn Pro Gly Ser Ser Thr Leu Leu Ala		
450	455	460
Met Glu Arg Ala Gly Asp Asn Ser Gln Ser Val Tyr Ile Pro Met Ser		
465	470	475
480		
Pro Gly Ala His His Phe Asp Ser Leu Gly Tyr Pro Ser Thr Thr Leu		
485	490	495
Pro Val His Arg Gly Pro Ser Arg Gly Ser Glu Ile Gln Pro Pro Pro		
500	505	510
Val Asn Arg Asn Leu Lys Pro Asp Arg Lys Ala Lys Pro Thr Pro Leu		
515	520	525
Asp Leu Arg Asn Asn Thr Val Ile Asp Glu Leu Pro Phe Lys Ser Pro		
530	535	540
Ile Thr Lys Ser Trp Ser Arg Ala Asn His Thr Phe Asn Ser Ser Ser		
545	550	555
560		
Ser Gln Tyr Cys Arg Pro Ile Ser Thr Gln Ser Ile Thr Ser Thr Asp		
565	570	575
Ser Gly Asp Ser Glu Glu Asn Tyr Val Pro Met Gln Asn Pro Val Ser		
580	585	590
Ala Ser Pro Val Pro Ser Gly Thr Asn Ser Pro Ala Pro Lys Lys Ser		
595	600	605
Thr Gly Ser Val Asp Tyr Leu Ala Leu Asp Phe Gln Pro Ser Xaa Pro		
610	615	620
Ser Pro His Arg Lys Pro Ser Thr Ser Ser Val Thr Ser Asp Glu Lys		
625	630	635
640		

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Val Asp Tyr Val Gln Val Asp Lys Glu Lys Thr Gln Ala Leu Gln Asn
645 650 655

Thr Met Gln Glu Trp Thr Asp Val Arg Gln Ser Ser Glu Pro Ser Lys
660 665 670

Gly Ala Lys Leu
675

<210> SEQ ID NO 16
<211> LENGTH: 169
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (18)..(18)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<400> SEQUENCE: 16

Met Cys His Ser Arg Ser Cys His Pro Thr Met Thr Ile Leu Gln Ala
1 5 10 15

Pro Xaa Pro Ala Pro Ser Thr Ile Pro Gly Pro Arg Arg Gly Ser Gly
20 25 30

Pro Glu Ile Phe Thr Phe Asp Pro Leu Pro Glu Pro Ala Ala Ala Pro
35 40 45

Ala Gly Arg Pro Ser Ala Ser Arg Gly His Arg Lys Arg Ser Arg Arg
50 55 60

Val Leu Tyr Pro Arg Val Val Arg Arg Gln Leu Pro Val Glu Glu Pro
65 70 75 80

Asn Pro Ala Lys Arg Leu Leu Phe Leu Leu Thr Ile Val Phe Cys
85 90 95

Gln Ile Leu Met Ala Glu Glu Gly Val Pro Ala Pro Leu Pro Pro Glu
100 105 110

Asp Ala Pro Asn Ala Ala Ser Leu Ala Pro Thr Pro Arg Ile Pro Asn
115 120 125

Trp Asp Phe Arg Gly Asn Leu Asn Ser Glu His Tyr Ser Gly Asp Ala
130 135 140

Thr Arg Cys Leu Arg Arg Asp Arg Gly Ala Gln Arg Pro Arg Arg Ile
145 150 155 160

Glu Thr Glu Ala Gln Pro Ser Trp Gly
165

<210> SEQ ID NO 17
<211> LENGTH: 630
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (223)..(223)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (320)..(320)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (602)..(602)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (607)..(607)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (616)..(616)

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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 17

Met Ala Ala Gly Val Ala Ala Trp Leu Pro Phe Ala Arg Ala Ala Ala			
1	5	10	15

Ile Gly Trp Met Pro Val Ala Ser Gly Pro Met Pro Ala Pro Pro Arg		
20	25	30

Gln Glu Arg Lys Arg Thr Gln Asp Ala Leu Ile Val Leu Asn Val Ser		
35	40	45

Gly Thr Arg Phe Gln Thr Trp Gln Asp Thr Leu Glu Arg Tyr Pro Asp		
50	55	60

Thr Leu Leu Gly Ser Ser Glu Arg Asp Phe Phe Tyr His Pro Glu Thr			
65	70	75	80

Gln Gln Tyr Phe Phe Asp Arg Asp Pro Asp Ile Phe Arg His Ile Leu		
85	90	95

Asn Phe Tyr Arg Thr Gly Lys Leu His Tyr Pro Arg His Glu Cys Ile		
100	105	110

Ser Ala Tyr Asp Glu Glu Leu Ala Phe Phe Gly Leu Ile Pro Glu Ile		
115	120	125

Ile Gly Asp Cys Cys Tyr Glu Glu Tyr Lys Asp Arg Arg Arg Glu Asn		
130	135	140

Ala Glu Arg Leu Gln Asp Asp Ala Asp Thr Asp Thr Ala Gly Glu Ser			
145	150	155	160

Ala Leu Pro Thr Met Thr Ala Arg Gln Arg Val Trp Arg Ala Phe Glu		
165	170	175

Asn Pro His Thr Ser Thr Met Ala Leu Val Phe Tyr Tyr Val Thr Gly		
180	185	190

Phe Phe Ile Ala Val Ser Val Ile Ala Asn Val Val Glu Thr Val Pro		
195	200	205

Cys Gly Ser Ser Pro Gly His Ile Lys Glu Leu Pro Cys Gly Xaa Arg		
210	215	220

Tyr Ala Val Ala Phe Phe Cys Leu Asp Thr Ala Cys Val Met Ile Phe			
225	230	235	240

Thr Val Glu Tyr Leu Leu Arg Leu Ala Ala Ala Pro Ser Arg Tyr Arg		
245	250	255

Phe Val Arg Ser Val Met Ser Ile Ile Asp Val Val Ala Ile Leu Pro		
260	265	270

Tyr Tyr Ile Gly Leu Val Met Thr Asp Asn Glu Asp Val Ser Gly Ala		
275	280	285

Phe Val Thr Leu Arg Val Phe Arg Val Phe Arg Ile Phe Lys Phe Ser		
290	295	300

Arg His Ser Gln Gly Leu Arg Ile Leu Gly Tyr Thr Leu Lys Ser Xaa			
305	310	315	320

Ala Ser Glu Leu Gly Phe Leu Leu Phe Ser Leu Thr Met Ala Ile Ile		
325	330	335

Ile Phe Ala Thr Val Met Phe Tyr Ala Glu Lys Gly Ser Ser Ala Ser		
340	345	350

Lys Phe Thr Ser Ile Pro Ala Ala Phe Trp Tyr Thr Ile Val Thr Met		
355	360	365

Thr Thr Leu Gly Tyr Gly Asp Met Val Pro Lys Thr Ile Ala Gly Lys		
370	375	380

Ile Phe Gly Ser Ile Cys Ser Leu Ser Gly Val Leu Val Ile Ala Leu			
385	390	395	400

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Pro Val Pro Val Ile Val Ser Asn Phe Ser Arg Ile Tyr His Gln Asn
405 410 415

Gln Arg Ala Asp Lys Arg Arg Ala Gln Lys Lys Ala Arg Leu Ala Arg
420 425 430

Ile Arg Ala Ala Lys Ser Gly Ser Ala Asn Ala Tyr Met Gln Ser Lys
435 440 445

Arg Asn Gly Leu Leu Ser Asn Gln Leu Gln Ser Ser Glu Asp Glu Gln
450 455 460

Ala Phe Val Ser Lys Ser Gly Ser Ser Phe Glu Thr Gln His His His
465 470 475 480

Leu Leu His Cys Leu Glu Lys Thr Thr Asn His Glu Phe Val Asp Glu
485 490 495

Gln Val Phe Glu Glu Ser Cys Met Glu Val Ala Thr Val Asn Arg Pro
500 505 510

Ser Ser His Ser Pro Ser Leu Ser Ser Gln Gln Gly Val Thr Ser Thr
515 520 525

Cys Cys Ser Arg Arg His Lys Lys Thr Phe Arg Ile Pro Asn Ala Asn
530 535 540

Val Ser Gly Ser His Gln Gly Ser Ile Gln Glu Leu Ser Thr Ile Gln
545 550 555 560

Ile Arg Cys Val Glu Arg Thr Pro Leu Ser Asn Ser Arg Ser Ser Leu
565 570 575

Asn Ala Lys Met Glu Glu Cys Val Lys Leu Asn Cys Glu Gln Pro Tyr
580 585 590

Val Thr Thr Ala Ile Ile Ser Ile Pro Xaa Pro Pro Val Thr Xaa Pro
595 600 605

Glu Gly Asp Asp Arg Pro Glu Xaa Pro Glu Tyr Ser Gly Gly Asn Ile
610 615 620

Val Arg Val Ser Ala Leu
625 630

<210> SEQ ID NO 18
<211> LENGTH: 744
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (389)..(389)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 18

Met Glu Gln Asp Pro Lys Pro Pro Arg Leu Arg Leu Trp Ala Leu Ile
1 5 10 15

Pro Trp Leu Pro Arg Lys Gln Arg Pro Arg Ile Ser Gln Thr Ser Leu
20 25 30

Pro Val Pro Gly Pro Gly Ser Gly Pro Gln Arg Asp Ser Asp Glu Gly
35 40 45

Val Leu Lys Glu Ile Ser Ile Thr His His Val Lys Ala Gly Ser Glu
50 55 60

Lys Ala Asp Pro Ser His Phe Glu Leu Leu Lys Val Leu Gly Gln Gly
65 70 75 80

Ser Phe Gly Lys Val Phe Leu Val Arg Lys Val Thr Arg Pro Asp Ser
85 90 95

Gly His Leu Tyr Ala Met Lys Val Leu Lys Ala Thr Leu Lys Val
100 105 110

Arg Asp Arg Val Arg Thr Lys Met Glu Arg Asp Ile Leu Ala Asp Val

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115	120	125
Asn His Pro Phe Val Val Lys Leu His Tyr Ala Phe Gln Thr Glu Gly		
130	135	140
Lys Leu Tyr Leu Ile Leu Asp Phe Leu Arg Gly Gly Asp Leu Phe Thr		
145	150	155
Arg Leu Ser Lys Glu Val Met Phe Thr Glu Glu Asp Val Lys Phe Tyr		
165	170	175
Leu Ala Glu Leu Ala Leu Gly Leu Asp His Leu His Ser Leu Gly Ile		
180	185	190
Ile Tyr Arg Asp Leu Lys Pro Glu Asn Ile Leu Leu Asp Glu Glu Gly		
195	200	205
His Ile Lys Leu Thr Asp Phe Gly Leu Ser Lys Glu Ala Ile Asp His		
210	215	220
Glu Lys Lys Ala Tyr Ser Phe Cys Gly Thr Val Glu Tyr Met Ala Pro		
225	230	235
Glu Val Val Asn Arg Gln Gly His Ser His Ser Ala Asp Trp Trp Ser		
245	250	255
Tyr Gly Val Leu Met Phe Glu Met Leu Thr Gly Ser Leu Pro Phe Gln		
260	265	270
Gly Lys Asp Arg Lys Glu Thr Met Thr Leu Ile Leu Lys Ala Lys Leu		
275	280	285
Gly Met Pro Gln Phe Leu Ser Thr Glu Ala Gln Ser Leu Leu Arg Ala		
290	295	300
Leu Phe Lys Arg Asn Pro Ala Asn Arg Leu Gly Ser Gly Pro Asp Gly		
305	310	315
320		
Ala Glu Glu Ile Lys Arg His Val Phe Tyr Ser Thr Ile Asp Trp Asn		
325	330	335
Lys Leu Tyr Arg Arg Glu Ile Lys Pro Pro Phe Lys Pro Ala Val Ala		
340	345	350
Gln Pro Asp Asp Thr Phe Tyr Phe Asp Thr Glu Phe Thr Ser Arg Thr		
355	360	365
Pro Lys Asp Ser Pro Gly Ile Pro Pro Ser Ala Gly Ala His Gln Leu		
370	375	380
Phe Arg Gly Phe Xaa Phe Val Ala Thr Gly Leu Met Glu Asp Asp Gly		
385	390	395
400		
Lys Pro Arg Ala Pro Gln Ala Pro Leu His Ser Val Val Gln Gln Leu		
405	410	415
His Gly Lys Asn Leu Val Phe Ser Asp Gly Tyr Val Val Lys Glu Thr		
420	425	430
Ile Gly Val Gly Ser Tyr Ser Glu Cys Lys Arg Cys Val His Lys Ala		
435	440	445
Thr Asn Met Glu Tyr Ala Val Lys Val Ile Asp Lys Ser Lys Arg Asp		
450	455	460
Pro Ser Glu Glu Ile Glu Ile Leu Leu Arg Tyr Gly Gln His Pro Asn		
465	470	475
480		
Ile Ile Thr Leu Lys Asp Val Tyr Asp Asp Gly Lys His Val Tyr Leu		
485	490	495
Val Thr Glu Leu Met Arg Gly Gly Glu Leu Leu Asp Lys Ile Leu Arg		
500	505	510
Gln Lys Phe Phe Ser Glu Arg Glu Ala Ser Phe Val Leu His Thr Ile		
515	520	525
Gly Lys Thr Val Glu Tyr Leu His Ser Gln Gly Val Val His Arg Asp		
530	535	540

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Leu Lys Pro Ser Asn Ile Leu Tyr Val Asp Glu Ser Gly Asn Pro Glu
 545 550 555 560

Cys Leu Arg Ile Cys Asp Phe Gly Phe Ala Lys Gln Leu Arg Ala Glu
 565 570 575

Asn Gly Leu Leu Met Thr Pro Cys Tyr Thr Ala Asn Phe Val Ala Pro
 580 585 590

Glu Val Leu Lys Arg Gln Gly Tyr Asp Glu Gly Cys Asp Ile Trp Ser
 595 600 605

Leu Gly Ile Leu Leu Tyr Thr Met Leu Ala Gly Tyr Thr Pro Phe Ala
 610 615 620

Asn Gly Pro Ser Asp Thr Pro Glu Glu Ile Leu Thr Arg Ile Gly Ser
 625 630 635 640

Gly Lys Phe Thr Leu Ser Gly Gly Asn Trp Asn Thr Val Ser Glu Thr
 645 650 655

Ala Lys Asp Leu Val Ser Lys Met Leu His Val Asp Pro His Gln Arg
 660 665 670

Leu Thr Ala Lys Gln Val Leu Gln His Pro Trp Val Thr Gln Lys Asp
 675 680 685

Lys Leu Pro Gln Ser Gln Leu Ser His Gln Asp Leu Gln Leu Val Lys
 690 695 700

Gly Ala Met Ala Ala Thr Tyr Ser Ala Leu Asn Ser Ser Lys Pro Thr
 705 710 715 720

Pro Gln Leu Lys Pro Ile Glu Ser Ser Ile Leu Ala Gln Arg Arg Val
 725 730 735

Arg Lys Leu Pro Ser Thr Thr Leu
 740

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<210> SEQ ID NO 19
<211> LENGTH: 557
<212> TYPE: PRT
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (83)..(83)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 19
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Met Asp Asp Leu Asp Ala Leu Leu Ala Asp Leu Glu Ser Thr Thr Ser
1 5 10 15

His Ile Ser Lys Arg Pro Val Phe Leu Ser Glu Glu Pro Pro Tyr Ser
20 25 30

Tyr Pro Thr Gly Asn His Thr Tyr Gln Glu Ile Ala Val Pro Pro Pro
35 40 45

Val Pro Pro Pro Ser Ser Glu Ala Leu Asn Gly Thr Val Leu Asp
50 55 60

Pro Leu Asp Gln Trp Gln Pro Ser Gly Ser Arg Tyr Ala His Gln Gln
65 70 75 80

Pro Pro Xaa Pro Leu Pro Val Tyr Ser Ser Ser Ala Lys Asn Ser Ser
85 90 95

Ala Ser Asn Thr Gln Asp Gly Val Gly Ser Leu Cys Ser Arg Ala Gly
100 105 110

Glu Glu Glu His Val Tyr Ser Phe Pro Asn Lys Gln Lys Ser Ala Glu
115 120 125

Pro Ser Pro Thr Val Met Ser Ser Ser Leu Gly Ser Asn Leu Ser Glu
130 135 140

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Leu Asp Arg Leu Leu Leu Glu Leu Asn Ala Val Gln His Ser Pro Pro
 145 150 155 160
 Gly Phe Pro Ala Asp Glu Ala Glu Ser Ser Pro Pro Leu Pro Gly Ala
 165 170 175
 Leu Ser Pro Leu Tyr Gly Ile Pro Glu Asn Asn Thr Pro Leu Gly Gly
 180 185 190
 Lys Ala Gly Pro Leu Val Lys Glu Lys Pro Lys Arg Asn Gly Gly Arg
 195 200 205
 Gly Leu Glu Asp Val Arg Pro Ser Val Glu Ser Leu Leu Asp Glu Leu
 210 215 220
 Glu Ser Ser Val Pro Ser Pro Val Pro Ala Ile Thr Val Asn Gln Gly
 225 230 235 240
 Glu Met Ser Ser Pro Gln Arg Val Thr Ser Ser Gln Gln Gln Thr Arg
 245 250 255
 Ile Ser Ala Ser Ser Ala Thr Arg Glu Leu Asp Glu Leu Met Ala Ser
 260 265 270
 Leu Ser Asp Phe Lys Phe Met Ala Gln Gly Lys Thr Gly Ser Ser Ser
 275 280 285
 Pro Pro Gly Gly Leu Ser Lys Pro Gly Ser Gln Leu Asp Ser Met Leu
 290 295 300
 Gly Ser Leu Gln Ser Asp Leu Asn Lys Leu Gly Val Ala Thr Val Ala
 305 310 315 320
 Lys Gly Val Cys Gly Ala Cys Lys Pro Ile Ala Gly Gln Val Val
 325 330 335
 Thr Ala Met Gly Lys Thr Trp His Pro Glu His Phe Val Cys Thr His
 340 345 350
 Cys Gln Glu Glu Ile Gly Ser Arg Asn Phe Phe Glu Arg Asp Gly Gln
 355 360 365
 Pro Tyr Cys Glu Lys Asp Tyr His Ser Leu Phe Ser Pro Arg Cys Tyr
 370 375 380
 Tyr Cys Asn Gly Pro Ile Leu Asp Lys Val Val Thr Ala Leu Asp Arg
 385 390 395 400
 Thr Trp His Pro Glu His Phe Phe Cys Ala Gln Cys Gly Ala Phe Phe
 405 410 415
 Gly Pro Glu Gly Phe His Glu Lys Asp Gly Lys Ala Tyr Cys Arg Lys
 420 425 430
 Asp Tyr Phe Asp Met Phe Ala Pro Lys Cys Gly Cys Ala Arg Ala
 435 440 445
 Ile Leu Glu Asn Tyr Ile Ser Ala Leu Asn Thr Leu Trp His Pro Glu
 450 455 460
 Cys Phe Val Cys Arg Glu Cys Phe Thr Pro Phe Val Asn Gly Ser Phe
 465 470 475 480
 Phe Glu His Asp Gly Gln Pro Tyr Cys Glu Val His Tyr His Glu Arg
 485 490 495
 Arg Gly Ser Leu Cys Ser Gly Cys Gln Lys Pro Ile Thr Gly Arg Cys
 500 505 510
 Ile Thr Ala Met Ala Lys Lys Phe His Pro Glu His Phe Val Cys Ala
 515 520 525
 Phe Cys Leu Lys Gln Leu Asn Lys Gly Thr Phe Lys Glu Gln Asn Asp
 530 535 540
 Lys Pro Tyr Cys Gln Ser Cys Phe Val Lys Leu Phe Cys
 545 550 555

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<210> SEQ_ID NO 20
<211> LENGTH: 1173
<212> TYPE: PRT
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (982)..(982)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 20

Met Ala Gly Ala Gln Pro Gly Val His Ala Leu Gln Leu Lys Pro Val
1           5          10          15

Cys Val Ser Asp Ser Leu Lys Lys Gly Thr Lys Leu Val Lys Trp Asp
20          25          30

Asp Asp Ser Thr Ile Val Thr Pro Thr Ile Leu Arg Thr Asp Pro Gln
35          40          45

Gly Phe Phe Phe Tyr Trp Thr Asp Gln Asn Lys Glu Thr Glu Leu Leu
50          55          60

Asp Leu Ser Leu Val Lys Asp Ala Arg Cys Gly Lys His Ala Glu Ala
65          70          75          80

Pro Lys Asp Pro Lys Leu Arg Glu Leu Leu Asp Val Gly Asn Ile Gly
85          90          95

His Leu Glu Gln Arg Met Ile Thr Val Val Tyr Gly Pro Asp Leu Ala
100         105         110

Asn Ile Ser His Leu Asn Leu Val Ala Phe Gln Glu Glu Val Ala Lys
115         120         125

Glu Trp Thr Asn Glu Val Phe Ser Leu Ala Thr Asn Leu Leu Ala Gln
130         135         140

Asn Met Ser Arg Asp Ala Phe Leu Glu Lys Ala Tyr Thr Lys Leu Lys
145         150         155         160

Leu Gln Val Thr Pro Glu Gly Arg Ile Pro Leu Lys Asn Ile Tyr Arg
165         170         175

Leu Phe Ser Ala Asp Arg Lys Arg Val Glu Thr Ala Leu Glu Ala Cys
180         185         190

Ser Leu Pro Ser Ser Arg Asn Asp Ser Ile Pro Gln Glu Asp Phe Thr
195         200         205

Pro Asp Val Tyr Arg Val Phe Leu Asn Asn Leu Cys Pro Arg Pro Glu
210         215         220

Ile Asp Asn Ile Phe Ser Glu Phe Gly Ala Lys Ser Lys Pro Tyr Leu
225         230         235         240

Thr Val Asp Gln Met Met Asp Phe Ile Asn Leu Lys Gln Arg Asp Pro
245         250         255

Arg Leu Asn Glu Ile Leu Tyr Pro Pro Leu Lys Gln Glu Val Gln
260         265         270

Val Leu Ile Glu Lys Tyr Glu Pro Asn Ser Ser Leu Ala Lys Lys Gly
275         280         285

Gln Met Ser Val Asp Gly Phe Met Arg Tyr Leu Ser Gly Glu Glu Asn
290         295         300

Gly Val Val Ser Pro Glu Lys Leu Asp Leu Asn Glu Asp Met Ser Gln
305         310         315         320

Pro Leu Ser His Tyr Phe Ile Asn Ser Ser His Asn Thr Tyr Leu Thr
325         330         335

Ala Gly Gln Leu Ala Gly Asn Ser Ser Val Glu Met Tyr Arg Gln Val
340         345         350

Leu Leu Ser Gly Cys Arg Cys Val Glu Leu Asp Cys Trp Lys Gly Arg
355         360         365

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Thr Ala Glu Glu Glu Pro Val Ile Thr His Gly Phe Thr Met Thr Thr
 370 375 380
 Glu Ile Ser Phe Lys Glu Val Ile Glu Ala Ile Ala Glu Cys Ala Phe
 385 390 395 400
 Lys Thr Ser Pro Phe Pro Ile Leu Leu Ser Phe Glu Asn His Val Asp
 405 410 415
 Ser Pro Lys Gln Gln Ala Lys Met Ala Glu Tyr Cys Arg Leu Ile Phe
 420 425 430
 Gly Asp Ala Leu Leu Met Glu Pro Leu Glu Lys Tyr Pro Leu Glu Ser
 435 440 445
 Gly Val Pro Leu Pro Ser Pro Met Asp Leu Met Tyr Lys Ile Leu Val
 450 455 460
 Lys Asn Lys Lys Ser His Lys Ser Ser Glu Gly Ser Gly Lys Lys
 465 470 475 480
 Lys Leu Ser Glu Gln Ala Ser Asn Thr Tyr Ser Asp Ser Ser Val
 485 490 495
 Phe Glu Pro Ser Ser Pro Gly Ala Gly Glu Ala Asp Thr Glu Ser Asp
 500 505 510
 Asp Asp Asp Asp Asp Asp Cys Lys Lys Ser Ser Met Asp Glu Gly
 515 520 525
 Thr Ala Gly Ser Glu Ala Met Ala Thr Glu Glu Met Ser Asn Leu Val
 530 535 540
 Asn Tyr Ile Gln Pro Val Lys Phe Glu Ser Phe Glu Ile Ser Lys Lys
 545 550 555 560
 Arg Asn Lys Ser Phe Glu Met Ser Ser Phe Val Glu Thr Lys Gly Leu
 565 570 575
 Glu Gln Leu Thr Lys Ser Pro Val Glu Phe Val Glu Tyr Asn Lys Met
 580 585 590
 Gln Leu Ser Arg Ile Tyr Pro Lys Gly Thr Arg Val Asp Ser Ser Asn
 595 600 605
 Tyr Met Pro Gln Leu Phe Trp Asn Ala Gly Cys Gln Met Met Ala Leu
 610 615 620
 Asn Phe Gln Thr Val Asp Leu Ala Met Gln Ile Asn Met Gly Met Tyr
 625 630 635 640
 Glu Tyr Asn Gly Lys Ser Gly Tyr Arg Leu Lys Pro Glu Phe Met Arg
 645 650 655
 Arg Pro Asp Lys His Phe Asp Pro Phe Thr Glu Gly Ile Val Asp Gly
 660 665 670
 Ile Val Ala Asn Thr Leu Ser Val Lys Ile Ile Ser Gly Gln Phe Leu
 675 680 685
 Ser Asp Lys Lys Val Gly Thr Tyr Val Glu Val Asp Met Phe Gly Leu
 690 695 700
 Pro Val Asp Thr Arg Arg Lys Ala Phe Thr Thr Lys Thr Ser Gln Gly
 705 710 715 720
 Asn Ala Val Asn Pro Val Trp Glu Glu Pro Ile Val Phe Lys Lys
 725 730 735
 Val Val Leu Pro Ser Leu Ala Cys Leu Arg Ile Ala Ala Tyr Glu Glu
 740 745 750
 Gly Gly Lys Phe Ile Gly His Arg Ile Leu Pro Val Gln Ala Ile Arg
 755 760 765
 Pro Gly Tyr His Tyr Ile Cys Leu Arg Asn Glu Arg Asn Gln Pro Leu
 770 775 780

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Thr Leu Pro Ala Val Phe Val Tyr Ile Glu Asp Lys Asp Tyr Val Pro
 785 790 795 800
 Asp Thr Tyr Ala Asp Val Ile Glu Ala Leu Ser Asn Pro Ile Arg Tyr
 805 810 815
 Val Asn Leu Met Glu Gln Arg Ala Lys Gln Leu Ala Ala Leu Thr Leu
 820 825 830
 Glu Asp Glu Glu Val Lys Lys Glu Ala Asp Pro Gly Glu Thr Ser
 835 840 845
 Ser Glu Ala Pro Ser Glu Thr Arg Thr Pro Ala Glu Asn Gly Val
 850 855 860
 Asn His Thr Ala Ser Leu Ala Pro Lys Pro Pro Ser Gln Ala Pro His
 865 870 875 880
 Ser Gln Pro Ala Pro Gly Ser Val Lys Ala Pro Ala Lys Thr Glu Asp
 885 890 895
 Leu Ile Gln Ser Val Leu Thr Glu Val Glu Ala Gln Thr Ile Glu Glu
 900 905 910
 Leu Lys Gln Gln Lys Ser Phe Val Lys Leu His Lys Lys His Tyr Lys
 915 920 925
 Glu Met Lys Asp Leu Val Lys Arg His His Lys Lys Thr Thr Glu Leu
 930 935 940
 Ile Lys Glu His Thr Thr Lys Tyr Asn Glu Ile Gln Ile Asp Tyr Leu
 945 950 955 960
 Arg Arg Arg Ala Ala Leu Glu Lys Ser Ala Lys Lys Asp Ser Lys Lys
 965 970 975
 Lys Ser Glu Pro Ser Xaa Pro Asp His Gly Ser Ser Ala Ile Glu Gln
 980 985 990
 Asp Leu Ala Ala Leu Asp Ala Glu Met Thr Gln Lys Leu Ile Asp Leu
 995 1000 1005
 Lys Asp Lys Gln Gln Gln Leu Leu Asn Leu Arg Gln Glu Gln
 1010 1015 1020
 Tyr Tyr Ser Glu Lys Tyr Gln Lys Arg Glu His Ile Lys Leu Leu
 1025 1030 1035
 Ile Gln Lys Leu Thr Asp Val Ala Glu Glu Cys Gln Asn Asn Gln
 1040 1045 1050
 Leu Lys Lys Leu Lys Glu Ile Cys Glu Lys Glu Lys Glu Leu
 1055 1060 1065
 Lys Lys Lys Met Asp Lys Lys Arg Gln Glu Lys Ile Thr Glu Ala
 1070 1075 1080
 Thr Ser Lys Asp Lys Ser Gln Met Glu Glu Lys Thr Glu Met
 1085 1090 1095
 Ile Arg Ser Tyr Ile Gln Glu Val Val Gln Tyr Ile Lys Arg Leu
 1100 1105 1110
 Glu Glu Ala Gln Ser Lys Arg Gln Glu Lys Leu Val Glu Lys His
 1115 1120 1125
 Asn Glu Ile Arg Gln Gln Ile Leu Asp Glu Lys Pro Lys Gly Glu
 1130 1135 1140
 Gly Pro Ser Ser Val Leu Ser Glu Gly Cys His Glu Asp Pro Ser
 1145 1150 1155
 Val Pro Pro Asn Phe Thr Pro Pro Asn Pro Gln Ala Leu Lys Trp
 1160 1165 1170

<210> SEQ ID NO 21
 <211> LENGTH: 443
 <212> TYPE: PRT

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<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (58)...(58)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (72)...(72)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (84)...(84)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 21

Met	Gln	Arg	Arg	Asp	Asp	Pro	Ala	Ala	Arg	Ser	Ser	Gly
1				5			10			15		

Arg	Ser	Gly	Ser	Met	Asp	Pro	Ser	Gly	Ala	His	Pro	Ser	Val	Arg	Gln
			20				25			30					

Thr	Pro	Ser	Arg	Gln	Pro	Pro	Leu	Pro	His	Arg	Ser	Arg	Gly	Gly	Gly
			35				40			45					

Gly	Gly	Ser	Arg	Gly	Gly	Ala	Arg	Ala	Xaa	Pro	Ala	Thr	Gln	Pro	Pro
			50			55			60						

Pro	Leu	Leu	Pro	Pro	Ser	Ala	Xaa	Gly	Pro	Asp	Ala	Thr	Val	Gly	Gly
65				70				75			80				

Pro	Ala	Pro	Xaa	Pro	Leu	Leu	Pro	Pro	Ser	Ala	Thr	Ala	Ser	Val	Lys
			85				90			95					

Met	Glu	Pro	Glu	Asn	Lys	Tyr	Leu	Pro	Glu	Leu	Met	Ala	Glu	Lys	Asp
			100				105			110					

Ser	Leu	Asp	Pro	Ser	Phe	Thr	His	Ala	Met	Gln	Leu	Leu	Thr	Ala	Glu
			115			120			125						

Ile	Glu	Lys	Ile	Gln	Lys	Gly	Asp	Ser	Lys	Lys	Asp	Asp	Glu	Glu	Asn
			130			135			140						

Tyr	Leu	Asp	Leu	Phe	Ser	His	Lys	Asn	Met	Lys	Leu	Lys	Glu	Arg	Val
145				150			155			160					

Leu	Ile	Pro	Val	Lys	Gln	Tyr	Pro	Lys	Phe	Asn	Phe	Val	Gly	Lys	Ile
			165				170			175					

Leu	Gly	Pro	Gln	Gly	Asn	Thr	Ile	Lys	Arg	Leu	Gln	Glu	Glu	Thr	Gly
			180			185			190						

Ala	Lys	Ile	Ser	Val	Leu	Gly	Lys	Gly	Ser	Met	Arg	Asp	Lys	Ala	Lys
			195			200			205						

Glu	Glu	Glu	Leu	Arg	Lys	Gly	Gly	Asp	Pro	Lys	Tyr	Ala	His	Leu	Asn
			210			215			220						

Met	Asp	Leu	His	Val	Phe	Ile	Glu	Val	Phe	Gly	Pro	Pro	Cys	Glu	Ala
225				230			235			240					

Tyr	Ala	Leu	Met	Ala	His	Ala	Met	Glu	Glu	Val	Lys	Lys	Phe	Leu	Val
			245			250			255						

Pro	Asp	Met	Met	Asp	Asp	Ile	Cys	Gln	Glu	Gln	Phe	Leu	Glu	Leu	Ser
			260				265			270					

Tyr	Leu	Asn	Gly	Val	Pro	Glu	Pro	Ser	Arg	Gly	Arg	Gly	Val	Pro	Val
			275			280			285						

Arg	Gly	Arg	Gly	Ala	Ala	Pro	Pro	Pro	Pro	Val	Pro	Arg	Gly	Arg	
			290			295			300						

Gly	Val	Gly	Pro	Pro	Arg	Gly	Ala	Leu	Val	Arg	Gly	Thr	Pro	Val	Arg
305				310			315			320					

Gly	Ala	Ile	Thr	Arg	Gly	Ala	Thr	Val	Thr	Arg	Gly	Val	Pro	Pro	Pro
			325			330			335						

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Pro Thr Val Arg Gly Ala Pro Ala Pro Arg Ala Arg Thr Ala Gly Ile
340 345 350

Gln Arg Ile Pro Leu Pro Pro Pro Ala Pro Glu Thr Tyr Glu Glu
355 360 365

Tyr Gly Tyr Asp Asp Thr Tyr Ala Glu Gln Ser Tyr Glu Gly Tyr Glu
370 375 380

Gly Tyr Tyr Ser Gln Ser Gln Gly Asp Ser Glu Tyr Tyr Asp Tyr Gly
385 390 395 400

His Gly Glu Val Gln Asp Ser Tyr Glu Ala Tyr Gly Gln Asp Asp Trp
405 410 415

Asn Gly Thr Arg Pro Ser Leu Lys Ala Pro Pro Ala Arg Pro Val Lys
420 425 430

Gly Ala Tyr Arg Glu His Pro Tyr Gly Arg Tyr
435 440

<210> SEQ ID NO 22
<211> LENGTH: 425
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (179)..(179)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (204)..(204)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (208)..(208)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 22

Met Ser Ser Ile Leu Pro Phe Thr Pro Pro Ile Val Lys Arg Leu Leu
1 5 10 15

Gly Trp Lys Lys Gly Glu Gln Asn Gly Gln Glu Glu Lys Trp Cys Glu
20 25 30

Lys Ala Val Lys Ser Leu Val Lys Lys Leu Lys Lys Thr Gly Gln Leu
35 40 45

Asp Glu Leu Glu Lys Ala Ile Thr Thr Gln Asn Val Asn Thr Lys Cys
50 55 60

Ile Thr Ile Pro Arg Ser Leu Asp Gly Arg Leu Gln Val Ser His Arg
65 70 75 80

Lys Gly Leu Pro His Val Ile Tyr Cys Arg Leu Trp Arg Trp Pro Asp
85 90 95

Leu His Ser His His Glu Leu Arg Ala Met Glu Leu Cys Glu Phe Ala
100 105 110

Phe Asn Met Lys Lys Asp Glu Val Cys Val Asn Pro Tyr His Tyr Gln
115 120 125

Arg Val Glu Thr Pro Val Leu Pro Pro Val Leu Val Pro Arg His Thr
130 135 140

Glu Ile Pro Ala Glu Phe Pro Pro Leu Asp Asp Tyr Ser His Ser Ile
145 150 155 160

Pro Glu Asn Thr Asn Phe Pro Ala Gly Ile Glu Pro Gln Ser Asn Ile
165 170 175

Pro Glu Xaa Pro Pro Pro Gly Tyr Leu Ser Glu Asp Gly Glu Thr Ser
180 185 190

Asp His Gln Met Asn His Ser Met Asp Ala Gly Xaa Pro Asn Leu Xaa
195 200 205

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Pro Asn Pro Met Ser Pro Ala His Asn Asn Leu Asp Leu Gln Pro Val
210 215 220

Thr Tyr Cys Glu Pro Ala Phe Trp Cys Ser Ile Ser Tyr Tyr Glu Leu
225 230 235 240

Asn Gln Arg Val Gly Glu Thr Phe His Ala Ser Gln Pro Ser Met Thr
245 250 255

Val Asp Gly Phe Thr Asp Pro Ser Asn Ser Glu Arg Phe Cys Leu Gly
260 265 270

Leu Leu Ser Asn Val Asn Arg Asn Ala Ala Val Glu Leu Thr Arg Arg
275 280 285

His Ile Gly Arg Gly Val Arg Leu Tyr Tyr Ile Gly Gly Glu Val Phe
290 295 300

Ala Glu Cys Leu Ser Asp Ser Ala Ile Phe Val Gln Ser Pro Asn Cys
305 310 315 320

Asn Gln Arg Tyr Gly Trp His Pro Ala Thr Val Cys Lys Ile Pro Pro
325 330 335

Gly Cys Asn Leu Lys Ile Phe Asn Asn Gln Glu Phe Ala Ala Leu Leu
340 345 350

Ala Gln Ser Val Asn Gln Gly Phe Glu Ala Val Tyr Gln Leu Thr Arg
355 360 365

Met Cys Thr Ile Arg Met Ser Phe Val Lys Gly Trp Gly Ala Glu Tyr
370 375 380

Arg Arg Gln Thr Val Thr Ser Thr Pro Cys Trp Ile Glu Leu His Leu
385 390 395 400

Asn Gly Pro Leu Gln Trp Leu Asp Lys Val Leu Thr Gln Met Gly Ser
405 410 415

Pro Ser Ile Arg Cys Ser Ser Val Ser
420 425

<210> SEQ ID NO 23
<211> LENGTH: 770
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (727) .. (727)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 23

Met Ala Gln Trp Asn Gln Leu Gln Leu Asp Thr Arg Tyr Leu Glu
1 5 10 15

Gln Leu His Gln Leu Tyr Ser Asp Ser Phe Pro Met Glu Leu Arg Gln
20 25 30

Phe Leu Ala Pro Trp Ile Glu Ser Gln Asp Trp Ala Tyr Ala Ala Ser
35 40 45

Lys Glu Ser His Ala Thr Leu Val Phe His Asn Leu Leu Gly Glu Ile
50 55 60

Asp Gln Gln Tyr Ser Arg Phe Leu Gln Glu Ser Asn Val Leu Tyr Gln
65 70 75 80

His Asn Leu Arg Arg Ile Lys Gln Phe Leu Gln Ser Arg Tyr Leu Glu
85 90 95

Lys Pro Met Glu Ile Ala Arg Ile Val Ala Arg Cys Leu Trp Glu Glu
100 105 110

Ser Arg Leu Leu Gln Thr Ala Ala Thr Ala Ala Gln Gln Gly Gly Gln
115 120 125

-continued

Ala Asn His Pro Thr Ala Ala Val Val Thr Glu Lys Gln Gln Met Leu
 130 135 140

Glu Gln His Leu Gln Asp Val Arg Lys Arg Val Gln Asp Leu Glu Gln
 145 150 155 160

Lys Met Lys Val Val Glu Asn Leu Gln Asp Asp Phe Asp Phe Asn Tyr
 165 170 175

Lys Thr Leu Lys Ser Gln Gly Asp Met Gln Asp Leu Asn Gly Asn Asn
 180 185 190

Gln Ser Val Thr Arg Gln Lys Met Gln Gln Leu Glu Gln Met Leu Thr
 195 200 205

Ala Leu Asp Gln Met Arg Arg Ser Ile Val Ser Glu Leu Ala Gly Leu
 210 215 220

Leu Ser Ala Met Glu Tyr Val Gln Lys Thr Leu Thr Asp Glu Glu Leu
 225 230 235 240

Ala Asp Trp Lys Arg Arg Gln Gln Ile Ala Cys Ile Gly Gly Pro Pro
 245 250 255

Asn Ile Cys Leu Asp Arg Leu Glu Asn Trp Ile Thr Ser Leu Ala Glu
 260 265 270

Ser Gln Leu Gln Thr Arg Gln Gln Ile Lys Lys Leu Glu Glu Leu Gln
 275 280 285

Gln Lys Val Ser Tyr Lys Gly Asp Pro Ile Val Gln His Arg Pro Met
 290 295 300

Leu Glu Glu Arg Ile Val Glu Leu Phe Arg Asn Leu Met Lys Ser Ala
 305 310 315 320

Phe Val Val Glu Arg Gln Pro Cys Met Pro Met His Pro Asp Arg Pro
 325 330 335

Leu Val Ile Lys Thr Gly Val Gln Phe Thr Thr Lys Val Arg Leu Leu
 340 345 350

Val Lys Phe Pro Glu Leu Asn Tyr Gln Leu Lys Ile Lys Val Cys Ile
 355 360 365

Asp Lys Asp Ser Gly Asp Val Ala Ala Leu Arg Gly Ser Arg Lys Phe
 370 375 380

Asn Ile Leu Gly Thr Asn Thr Lys Val Met Asn Met Glu Glu Ser Asn
 385 390 395 400

Asn Gly Ser Leu Ser Ala Glu Phe Lys His Leu Thr Leu Arg Glu Gln
 405 410 415

Arg Cys Gly Asn Gly Gly Arg Ala Asn Cys Asp Ala Ser Leu Ile Val
 420 425 430

Thr Glu Glu Leu His Leu Ile Thr Phe Glu Thr Glu Val Tyr His Gln
 435 440 445

Gly Leu Lys Ile Asp Leu Glu Thr His Ser Leu Pro Val Val Ile
 450 455 460

Ser Asn Ile Cys Gln Met Pro Asn Ala Trp Ala Ser Ile Leu Trp Tyr
 465 470 475 480

Asn Met Leu Thr Asn Asn Pro Lys Asn Val Asn Phe Phe Thr Lys Pro
 485 490 495

Pro Ile Gly Thr Trp Asp Gln Val Ala Glu Val Leu Ser Trp Gln Phe
 500 505 510

Ser Ser Thr Thr Lys Arg Gly Leu Ser Ile Glu Gln Leu Thr Thr Leu
 515 520 525

Ala Glu Lys Leu Leu Gly Pro Gly Val Asn Tyr Ser Gly Cys Gln Ile
 530 535 540

Thr Trp Ala Lys Phe Cys Lys Glu Asn Met Ala Gly Lys Gly Phe Ser

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545	550	555	560
Phe Trp Val Trp Leu Asp Asn Ile Ile Asp Leu Val Lys Lys Tyr Ile			
565	570	575	
Leu Ala Leu Trp Asn Glu Gly Tyr Ile Met Gly Phe Ile Ser Lys Glu			
580	585	590	
Arg Glu Arg Ala Ile Leu Ser Thr Lys Pro Pro Gly Thr Phe Leu Leu			
595	600	605	
Arg Phe Ser Glu Ser Ser Lys Glu Gly Gly Val Thr Phe Thr Trp Val			
610	615	620	
Glu Lys Asp Ile Ser Gly Lys Thr Gln Ile Gln Ser Val Glu Pro Tyr			
625	630	635	640
Thr Lys Gln Gln Leu Asn Asn Met Ser Phe Ala Glu Ile Ile Met Gly			
645	650	655	
Tyr Lys Ile Met Asp Ala Thr Asn Ile Leu Val Ser Pro Leu Val Tyr			
660	665	670	
Leu Tyr Pro Asp Ile Pro Lys Glu Ala Phe Gly Lys Tyr Cys Arg			
675	680	685	
Pro Glu Ser Gln Glu His Pro Glu Ala Asp Pro Gly Ser Ala Ala Pro			
690	695	700	
Tyr Leu Lys Thr Lys Phe Ile Cys Val Thr Pro Thr Thr Cys Ser Asn			
705	710	715	720
Thr Ile Asp Leu Pro Met Xaa Pro Arg Thr Leu Asp Ser Leu Met Gln			
725	730	735	
Phe Gly Asn Asn Gly Glu Ala Glu Pro Ser Ala Gly Gly Gln Phe			
740	745	750	
Glu Ser Leu Thr Phe Asp Met Glu Leu Thr Ser Glu Cys Ala Thr Ser			
755	760	765	
Pro Met			
770			

<210> SEQ_ID NO 24
 <211> LENGTH: 824
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <221> NAME/KEY: misc_feature
 <222> LOCATION: (735)..(735)
 <223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 24

Met Arg Gln Ser Leu Leu Phe Leu Thr Ser Val Val Pro Phe Val Leu			
1	5	10	15
Ala Pro Arg Pro Pro Asp Asp Pro Gly Phe Gly Pro His Gln Arg Leu			
20	25	30	
Glu Lys Leu Asp Ser Leu Leu Ser Asp Tyr Asp Ile Leu Ser Leu Ser			
35	40	45	
Asn Ile Gln Gln His Ser Val Arg Lys Arg Asp Leu Gln Thr Ser Thr			
50	55	60	
His Val Glu Thr Leu Leu Thr Phe Ser Ala Leu Lys Arg His Phe Lys			
65	70	75	80
Leu Tyr Leu Thr Ser Ser Thr Glu Arg Phe Ser Gln Asn Phe Lys Val			
85	90	95	
Val Val Val Asp Gly Lys Asn Glu Ser Glu Tyr Thr Val Lys Trp Gln			
100	105	110	
Asp Phe Phe Thr Gly His Val Val Gly Glu Pro Asp Ser Arg Val Leu			
115	120	125	

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Ala His Ile Arg Asp Asp Asp Val Ile Ile Arg Ile Asn Thr Asp Gly
 130 135 140
 Ala Glu Tyr Asn Ile Glu Pro Leu Trp Arg Phe Val Asn Asp Thr Lys
 145 150 155 160
 Asp Lys Arg Met Leu Val Tyr Lys Ser Glu Asp Ile Lys Asn Val Ser
 165 170 175
 Arg Leu Gln Ser Pro Lys Val Cys Gly Tyr Leu Lys Val Asp Asn Glu
 180 185 190
 Glu Leu Leu Pro Lys Gly Leu Val Asp Arg Glu Pro Pro Glu Glu Leu
 195 200 205
 Val His Arg Val Lys Arg Arg Ala Asp Pro Asp Pro Met Lys Asn Thr
 210 215 220
 Cys Lys Leu Leu Val Val Ala Asp His Arg Phe Tyr Arg Tyr Met Gly
 225 230 235 240
 Arg Gly Glu Ser Thr Thr Asn Tyr Leu Ile Glu Leu Ile Asp
 245 250 255
 Arg Val Asp Asp Ile Tyr Arg Asn Thr Ser Trp Asp Asn Ala Gly Phe
 260 265 270
 Lys Gly Tyr Gly Ile Gln Ile Glu Gln Ile Arg Ile Leu Lys Ser Pro
 275 280 285
 Gln Glu Val Lys Pro Gly Glu Lys His Tyr Asn Met Ala Lys Ser Tyr
 290 295 300
 Pro Asn Glu Glu Lys Asp Ala Trp Asp Val Lys Met Leu Leu Glu Gln
 305 310 315 320
 Phe Ser Phe Asp Ile Ala Glu Glu Ala Ser Lys Val Cys Leu Ala His
 325 330 335
 Leu Phe Thr Tyr Gln Asp Phe Asp Met Gly Thr Leu Gly Leu Ala Tyr
 340 345 350
 Val Gly Ser Pro Arg Ala Asn Ser His Gly Gly Val Cys Pro Lys Ala
 355 360 365
 Tyr Tyr Ser Pro Val Gly Lys Lys Asn Ile Tyr Leu Asn Ser Gly Leu
 370 375 380
 Thr Ser Thr Lys Asn Tyr Gly Lys Thr Ile Leu Thr Lys Glu Ala Asp
 385 390 395 400
 Leu Val Thr Thr His Glu Leu Gly His Asn Phe Gly Ala Glu His Asp
 405 410 415
 Pro Asp Gly Leu Ala Glu Cys Ala Pro Asn Glu Asp Gln Gly Lys
 420 425 430
 Tyr Val Met Tyr Pro Ile Ala Val Ser Gly Asp His Glu Asn Asn Lys
 435 440 445
 Met Phe Ser Asn Cys Ser Lys Gln Ser Ile Tyr Lys Thr Ile Glu Ser
 450 455 460
 Lys Ala Gln Glu Cys Phe Gln Glu Arg Ser Asn Lys Val Cys Gly Asn
 465 470 475 480
 Ser Arg Val Asp Glu Gly Glu Glu Cys Asp Pro Gly Ile Met Tyr Leu
 485 490 495
 Asn Asn Asp Thr Cys Cys Asn Ser Asp Cys Thr Leu Lys Glu Gly Val
 500 505 510
 Gln Cys Ser Asp Arg Asn Ser Pro Cys Cys Lys Asn Cys Gln Phe Glu
 515 520 525
 Thr Ala Gln Lys Lys Cys Gln Glu Ala Ile Asn Ala Thr Cys Lys Gly
 530 535 540

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Val Ser Tyr Cys Thr Gly Asn Ser Ser Glu Cys Pro Pro Pro Gly Asn
 545 550 555 560
 Ala Glu Asp Asp Thr Val Cys Leu Asp Leu Gly Lys Cys Lys Asp Gly
 565 570 575
 Lys Cys Ile Pro Phe Cys Glu Arg Gln Gln Leu Glu Ser Cys Ala
 580 585 590
 Cys Asn Glu Thr Asp Asn Ser Cys Lys Val Cys Cys Arg Asp Leu Ser
 595 600 605
 Gly Arg Cys Val Pro Tyr Val Asp Ala Glu Gln Lys Asn Leu Phe Leu
 610 615 620
 Arg Lys Gly Lys Pro Cys Thr Val Gly Phe Cys Asp Met Asn Gly Lys
 625 630 635 640
 Cys Glu Lys Arg Val Gln Asp Val Ile Glu Arg Phe Trp Asp Phe Ile
 645 650 655
 Asp Gln Leu Ser Ile Asn Thr Phe Gly Lys Phe Leu Ala Asp Asn Ile
 660 665 670
 Val Gly Ser Val Leu Val Phe Ser Leu Ile Phe Trp Ile Pro Phe Ser
 675 680 685
 Ile Leu Val His Cys Val Asp Lys Lys Leu Asp Lys Gln Tyr Glu Ser
 690 695 700
 Leu Ser Leu Phe His Pro Ser Asn Val Glu Met Leu Ser Ser Met Asp
 705 710 715 720
 Ser Ala Ser Val Arg Ile Ile Lys Pro Phe Pro Ala Pro Gln Xaa Pro
 725 730 735
 Gly Arg Leu Gln Pro Ala Pro Val Ile Pro Ser Ala Pro Ala Ala Pro
 740 745 750
 Lys Leu Asp His Gln Arg Met Asp Thr Ile Gln Glu Asp Pro Ser Thr
 755 760 765
 Asp Ser His Met Asp Glu Asp Gly Phe Glu Lys Asp Pro Phe Pro Asn
 770 775 780
 Ser Ser Thr Ala Ala Lys Ser Phe Glu Asp Leu Thr Asp His Pro Val
 785 790 795 800
 Thr Arg Ser Glu Lys Ala Ala Ser Phe Lys Leu Gln Arg Gln Asn Arg
 805 810 815
 Val Asp Ser Lys Glu Thr Glu Cys
 820

<210> SEQ_ID NO 25
 <211> LENGTH: 1581
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <221> NAME/KEY: misc_feature
 <222> LOCATION: (1032)...(1032)
 <223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
 <220> FEATURE:
 <221> NAME/KEY: misc_feature
 <222> LOCATION: (1457)...(1457)
 <223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 25

 Met Lys Ala Gln Gly Glu Thr Glu Glu Ser Glu Lys Leu Ser Lys Met
 1 5 10 15

 Ser Ser Leu Leu Glu Arg Leu His Ala Lys Phe Asn Gln Asn Arg Pro
 20 25 30

 Trp Ser Glu Thr Ile Lys Leu Val Arg Gln Val Met Glu Lys Arg Val
 35 40 45

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Val	Met	Ser	Ser	Gly	Gly	His	Gln	His	Leu	Val	Ser	Cys	Leu	Glu	Thr
50															
														60	

Leu	Gln	Lys	Ala	Leu	Lys	Val	Thr	Ser	Leu	Pro	Ala	Met	Thr	Asp	Arg
65															80

Leu	Glu	Ser	Ile	Ala	Arg	Gln	Asn	Gly	Leu	Gly	Ser	His	Leu	Ser	Ala	
														85	90	95

Ser	Gly	Thr	Glu	Cys	Tyr	Ile	Thr	Ser	Asp	Met	Phe	Tyr	Val	Glu	Val	
														100	105	110

Gln	Leu	Asp	Pro	Ala	Gly	Gln	Leu	Cys	Asp	Val	Lys	Val	Ala	His	His	
														115	120	125

Gly	Glu	Asn	Pro	Val	Ser	Cys	Pro	Glu	Leu	Val	Gln	Gln	Leu	Arg	Glu	
														130	135	140

Lys	Asn	Phe	Asp	Glu	Phe	Ser	Lys	His	Leu	Lys	Gly	Leu	Val	Asn	Leu		
														145	150	155	160

Tyr	Asn	Leu	Pro	Gly	Asp	Asn	Lys	Leu	Lys	Thr	Lys	Met	Tyr	Leu	Ala	
														165	170	175

Leu	Gln	Ser	Leu	Glu	Gln	Asp	Leu	Ser	Lys	Met	Ala	Ile	Met	Tyr	Trp	
														180	185	190

Lys	Ala	Thr	Asn	Ala	Gly	Pro	Leu	Asp	Lys	Ile	Leu	His	Gly	Ser	Val	
														195	200	205

Gly	Tyr	Leu	Thr	Pro	Arg	Ser	Gly	Gly	His	Leu	Met	Asn	Leu	Lys	Tyr	
														210	215	220

Tyr	Val	Ser	Pro	Ser	Asp	Leu	Leu	Asp	Asp	Lys	Thr	Ala	Ser	Pro	Ile		
														225	230	235	240

Ile	Leu	His	Glu	Asn	Asn	Val	Ser	Arg	Ser	Leu	Gly	Met	Asn	Ala	Ser	
														245	250	255

Val	Thr	Ile	Glu	Gly	Thr	Ser	Ala	Val	Tyr	Lys	Leu	Pro	Ile	Ala	Pro	
														260	265	270

Leu	Ile	Met	Gly	Ser	His	Pro	Val	Asp	Asn	Lys	Trp	Thr	Pro	Ser	Phe	
														275	280	285

Ser	Ser	Ile	Thr	Ser	Ala	Asn	Ser	Val	Asp	Leu	Pro	Ala	Cys	Phe	Phe	
														290	295	300

Leu	Lys	Phe	Pro	Gln	Pro	Ile	Pro	Val	Ser	Arg	Ala	Phe	Val	Gln	Lys		
														305	310	315	320

Leu	Gln	Asn	Cys	Thr	Gly	Ile	Pro	Leu	Phe	Glu	Thr	Gln	Pro	Thr	Tyr	
														325	330	335

Ala	Pro	Leu	Tyr	Glu	Leu	Ile	Thr	Gln	Phe	Glu	Leu	Ser	Lys	Asp	Pro	
														340	345	350

Asp	Pro	Ile	Pro	Leu	Asn	His	Asn	Met	Arg	Phe	Tyr	Ala	Ala	Leu	Pro	
														355	360	365

Gly	Gln	Gln	His	Cys	Tyr	Phe	Leu	Asn	Lys	Asp	Ala	Pro	Leu	Pro	Asp	
														370	375	380

Gly	Arg	Ser	Leu	Gln	Gly	Thr	Leu	Val	Ser	Lys	Ile	Thr	Phe	Gln	His		
														385	390	395	400

Pro	Gly	Arg	Val	Pro	Leu	Ile	Leu	Asn	Leu	Ile	Arg	His	Gln	Val	Ala	
														405	410	415

Tyr	Asn	Thr	Leu	Ile	Gly	Ser	Cys	Val	Lys	Arg	Thr	Ile	Leu	Lys	Glu	
														420	425	430

Asp	Ser	Pro	Gly	Leu	Leu	Gln	Phe	Glu	Val	Cys	Pro	Leu	Ser	Glu	Ser	
														435	440	445

Arg	Phe	Ser	Val	Ser	Phe	Gln	His	Pro	Val	Asn	Asp	Ser	Leu	Val	Cys	
														450	455	460

Val Val Met Asp Val Gln Asp Ser Thr His Val Ser Cys Lys Leu Tyr

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465	470	475	480
Lys Gly Leu Ser Asp Ala Leu Ile Cys Thr Asp Asp Phe Ile Ala Lys			
485	490	495	
Val Val Gln Arg Cys Met Ser Ile Pro Val Thr Met Arg Ala Ile Arg			
500	505	510	
Arg Lys Ala Glu Thr Ile Gln Ala Asp Thr Pro Ala Leu Ser Leu Ile			
515	520	525	
Ala Glu Thr Val Glu Asp Met Val Lys Lys Asn Leu Pro Pro Ala Ser			
530	535	540	
Ser Pro Gly Tyr Gly Met Thr Thr Gly Asn Asn Pro Met Ser Gly Thr			
545	550	555	560
Thr Thr Ser Thr Asn Thr Phe Pro Gly Gly Pro Ile Ala Thr Leu Phe			
565	570	575	
Asn Met Ser Met Ser Ile Lys Asp Arg His Glu Ser Val Gly His Gly			
580	585	590	
Glu Asp Phe Ser Lys Val Ser Gln Asn Pro Ile Leu Thr Ser Leu Leu			
595	600	605	
Gln Ile Thr Gly Asn Gly Gly Ser Thr Ile Gly Ser Ser Pro Thr Pro			
610	615	620	
Pro His His Thr Pro Pro Pro Val Ser Ser Met Ala Gly Asn Thr Lys			
625	630	635	640
Asn His Pro Met Leu Met Asn Leu Leu Lys Asp Asn Pro Ala Gln Asp			
645	650	655	
Phe Ser Thr Leu Tyr Gly Ser Ser Pro Leu Glu Arg Gln Asn Ser Ser			
660	665	670	
Ser Gly Ser Pro Arg Met Glu Ile Cys Ser Gly Ser Asn Lys Thr Lys			
675	680	685	
Lys Lys Lys Ser Ser Arg Leu Pro Pro Glu Lys Pro Lys His Gln Thr			
690	695	700	
Glu Asp Asp Phe Gln Arg Glu Leu Phe Ser Met Asp Val Asp Ser Gln			
705	710	715	720
Asn Pro Ile Phe Asp Val Asn Met Thr Ala Asp Thr Leu Asp Thr Pro			
725	730	735	
His Ile Thr Pro Ala Pro Ser Gln Cys Ser Thr Pro Pro Thr Thr Tyr			
740	745	750	
Pro Gln Pro Val Pro His Pro Gln Pro Ser Ile Gln Arg Met Val Arg			
755	760	765	
Leu Ser Ser Ser Asp Ser Ile Gly Pro Asp Val Thr Asp Ile Leu Ser			
770	775	780	
Asp Ile Ala Glu Glu Ala Ser Lys Leu Pro Ser Thr Ser Asp Asp Cys			
785	790	795	800
Pro Ala Ile Gly Thr Pro Leu Arg Asp Ser Ser Ser Ser Gly His Ser			
805	810	815	
Gln Ser Thr Leu Phe Asp Ser Asp Val Phe Gln Thr Asn Asn Asn Glu			
820	825	830	
Asn Pro Tyr Thr Asp Pro Ala Asp Leu Ile Ala Asp Ala Ala Gly Ser			
835	840	845	
Pro Ser Ser Asp Ser Pro Thr Asn His Phe Phe His Asp Gly Val Asp			
850	855	860	
Phe Asn Pro Asp Leu Leu Asn Ser Gln Ser Gln Ser Gly Phe Gly Glu			
865	870	875	880
Glu Tyr Phe Asp Glu Ser Ser Gln Ser Gly Asp Asn Asp Asp Phe Lys			
885	890	895	

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Gly Phe Ala Ser Gln Ala Leu Asn Thr Leu Gly Val Pro Met Leu Gly
900 905 910

Gly Asp Asn Gly Glu Thr Lys Phe Lys Gly Asn Asn Gln Ala Asp Thr
915 920 925

Val Asp Phe Ser Ile Ile Ser Val Ala Gly Lys Ala Leu Ala Pro Ala
930 935 940

Asp Leu Met Glu His His Ser Gly Ser Gln Gly Pro Leu Leu Thr Thr
945 950 955 960

Gly Asp Leu Gly Lys Glu Lys Thr Gln Lys Arg Val Lys Glu Gly Asn
965 970 975

Gly Thr Ser Asn Ser Thr Leu Ser Gly Pro Gly Leu Asp Ser Lys Pro
980 985 990

Gly Lys Arg Ser Arg Thr Pro Ser Asn Asp Gly Lys Ser Lys Asp Lys
995 1000 1005

Pro Pro Lys Arg Lys Lys Ala Asp Thr Glu Gly Lys Ser Pro Ser
1010 1015 1020

His Ser Ser Ser Asn Arg Pro Phe Xaa Pro Pro Thr Ser Thr Gly
1025 1030 1035

Gly Ser Lys Ser Pro Gly Ser Ala Gly Arg Ser Gln Thr Pro Pro
1040 1045 1050

Gly Val Ala Thr Pro Pro Ile Pro Lys Ile Thr Ile Gln Ile Pro
1055 1060 1065

Lys Gly Thr Val Met Val Gly Lys Pro Ser Ser His Ser Gln Tyr
1070 1075 1080

Thr Ser Ser Gly Ser Val Ser Ser Ser Gly Ser Lys Ser His His
1085 1090 1095

Ser His Ser Ser Ser Ser Ser Ala Ser Thr Ser Gly Lys
1100 1105 1110

Met Lys Ser Ser Lys Ser Glu Gly Ser Ser Ser Ser Lys Leu Ser
1115 1120 1125

Ser Ser Met Tyr Ser Ser Gln Gly Ser Ser Gly Ser Ser Gln Ser
1130 1135 1140

Lys Asn Ser Ser Gln Ser Gly Lys Pro Gly Ser Ser Pro Ile
1145 1150 1155

Thr Lys His Gly Leu Ser Ser Gly Ser Ser Ser Thr Lys Met Lys
1160 1165 1170

Pro Gln Gly Lys Pro Ser Ser Leu Met Asn Pro Ser Leu Ser Lys
1175 1180 1185

Pro Asn Ile Ser Pro Ser His Ser Arg Pro Pro Gly Gly Ser Asp
1190 1195 1200

Lys Leu Ala Ser Pro Met Lys Pro Val Pro Gly Thr Pro Pro Ser
1205 1210 1215

Ser Lys Ala Lys Ser Pro Ile Ser Ser Gly Ser Gly Ser His
1220 1225 1230

Met Ser Gly Thr Ser Ser Ser Gly Met Lys Ser Ser Ser Gly
1235 1240 1245

Leu Gly Ser Ser Gly Ser Leu Ser Gln Lys Thr Pro Pro Ser Ser
1250 1255 1260

Asn Ser Cys Thr Ala Ser Ser Ser Ser Phe Ser Ser Ser Gly Ser
1265 1270 1275

Ser Met Ser Ser Ser Gln Asn Gln His Gly Ser Ser Lys Gly Lys
1280 1285 1290

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Ser	Pro	Ser	Arg	Asn	Lys	Lys	Pro	Ser	Leu	Thr	Ala	Val	Ile	Asp	
1295					1300						1305				
Lys	Leu	Lys	His	Gly	Val	Val	Thr	Ser	Gly	Pro	Gly	Gly	Glu	Asp	
1310					1315						1320				
Pro	Leu	Asp	Gly	Gln	Met	Gly	Val	Ser	Thr	Asn	Ser	Ser	Ser	His	
1325					1330						1335				
Pro	Met	Ser	Ser	Lys	His	Asn	Met	Ser	Gly	Gly	Glu	Phe	Gln	Gly	
1340					1345						1350				
Lys	Arg	Glu	Lys	Ser	Asp	Lys	Asp	Lys	Ser	Lys	Val	Ser	Thr	Ser	
1355					1360						1365				
Gly	Ser	Ser	Val	Asp	Ser	Ser	Lys	Lys	Thr	Ser	Glu	Ser	Lys	Asn	
1370					1375						1380				
Val	Gly	Ser	Ser	Thr	Gly	Val	Ala	Lys	Ile	Ile	Ile	Ser	Lys	His	Asp
1385					1390						1395				
Gly	Gly	Ser	Pro	Ser	Ile	Lys	Ala	Lys	Val	Thr	Leu	Gln	Lys	Pro	
1400					1405						1410				
Gly	Glu	Ser	Ser	Gly	Glu	Gly	Leu	Arg	Pro	Gln	Met	Ala	Ser	Ser	
1415					1420						1425				
Lys	Asn	Tyr	Gly	Ser	Pro	Leu	Ile	Ser	Gly	Ser	Thr	Pro	Lys	His	
1430					1435						1440				
Glu	Arg	Gly	Ser	Pro	Ser	His	Ser	Lys	Ser	Pro	Ala	Tyr	Xaa	Pro	
1445					1450						1455				
Gln	Asn	Leu	Asp	Ser	Glu	Ser	Glu	Ser	Gly	Ser	Ser	Ile	Ala	Glu	
1460					1465						1470				
Lys	Ser	Tyr	Gln	Asn	Ser	Pro	Ser	Ser	Asp	Asp	Gly	Ile	Arg	Pro	
1475					1480						1485				
Leu	Pro	Glu	Tyr	Ser	Thr	Glu	Lys	His	Lys	His	Lys	Lys	Glu		
1490					1495						1500				
Lys	Lys	Lys	Val	Lys	Asp	Lys	Asp	Arg	Asp	Arg	Asp	Arg	Asp	Lys	
1505					1510						1515				
Asp	Arg	Asp	Lys	Lys	Ser	His	Ser	Ile	Lys	Pro	Glu	Ser	Trp		
1520					1525						1530				
Ser	Lys	Ser	Pro	Ile	Ser	Ser	Asp	Gln	Ser	Leu	Ser	Met	Thr	Ser	
1535					1540						1545				
Asn	Thr	Ile	Leu	Ser	Ala	Asp	Arg	Pro	Ser	Arg	Leu	Ser	Pro	Asp	
1550					1555						1560				
Phe	Met	Ile	Gly	Glu	Glu	Asp	Asp	Asp	Leu	Met	Asp	Val	Ala	Leu	
1565					1570						1575				
Ile	Gly	Asn													
		1580													

<210> SEQ ID NO 26
<211> LENGTH: 372
<212> TYPE: PRT
<213> ORGANISM: mouse
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (18)...(18)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (328)...(328)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (337)...(337)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<400> SEQUENCE: 26

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Met Ser Met Ser Pro Lys His Thr Thr Pro Phe Ser Val Ser Asp Ile
 1 5 10 15
 Leu Xaa Pro Leu Glu Glu Ser Tyr Lys Lys Val Gly Met Glu Gly Gly
 20 25 30
 Gly Leu Gly Ala Pro Leu Ala Ala Tyr Arg Gln Gly Gln Ala Ala Pro
 35 40 45
 Pro Ala Ala Ala Met Gln Gln His Ala Val Gly His His Gly Ala Val
 50 55 60
 Thr Ala Ala Tyr His Met Thr Ala Ala Gly Val Pro Gln Leu Ser His
 65 70 75 80
 Ser Ala Val Gly Gly Tyr Cys Asn Gly Asn Leu Gly Asn Met Ser Glu
 85 90 95
 Leu Pro Pro Tyr Gln Asp Thr Met Arg Asn Ser Ala Ser Gly Pro Gly
 100 105 110
 Trp Tyr Gly Ala Asn Pro Asp Pro Arg Phe Pro Ala Ile Ser Arg Phe
 115 120 125
 Met Gly Pro Ala Ser Gly Met Asn Met Ser Gly Met Gly Gly Leu Gly
 130 135 140
 Ser Leu Gly Asp Val Ser Lys Asn Met Ala Pro Leu Pro Ser Ala Pro
 145 150 155 160
 Arg Arg Lys Arg Arg Val Leu Phe Ser Gln Ala Gln Val Tyr Glu Leu
 165 170 175
 Glu Arg Arg Phe Lys Gln Gln Lys Tyr Leu Ser Ala Pro Glu Arg Glu
 180 185 190
 His Leu Ala Ser Met Ile His Leu Thr Pro Thr Gln Val Lys Ile Trp
 195 200 205
 Phe Gln Asn His Arg Tyr Lys Met Lys Arg Gln Ala Lys Asp Lys Ala
 210 215 220
 Ala Gln Gln Gln Leu Gln Gln Asp Ser Gly Gly Gly Gly Gly Gly
 225 230 235 240
 Gly Gly Ala Gly Cys Pro Gln Gln Gln Ala Gln Gln Ser Pro
 245 250 255
 Arg Arg Val Ala Val Pro Val Leu Val Lys Asp Gly Lys Pro Cys Gln
 260 265 270
 Ala Gly Ala Pro Ala Pro Gly Ala Ala Ser Leu Gln Ser His Ala Gln
 275 280 285
 Gln Gln Ala Gln Gln Gln Ala Gln Ala Ala Gln Ala Ala Ala Ala
 290 295 300
 Ile Ser Val Gly Ser Gly Gly Ala Val Leu Gly Ala His Pro Gly His
 305 310 315 320
 Gln Pro Gly Ser Ala Gly Gln Xaa Pro Asp Leu Ala His His Ala Ala
 325 330 335
 Xaa Pro Ala Gly Leu Gln Gly Gln Val Ser Ser Leu Ser His Leu Asn
 340 345 350
 Ser Ser Gly Ser Asp Tyr Gly Ala Met Ser Cys Ser Thr Leu Leu Tyr
 355 360 365
 Gly Arg Thr Trp
 370

<210> SEQ ID NO 27
 <211> LENGTH: 498
 <212> TYPE: PRT
 <213> ORGANISM: rat
 <220> FEATURE:

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<221> NAME/KEY: misc_feature
 <222> LOCATION: (31)..(31)
 <223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 27

Met	Pro	Thr	Pro	Ser	Ala	Pro	Ser	Pro	Gln	Pro	Lys	Gly	Phe	Arg	Arg
1															
														15	

Ala	Val	Ser	Glu	Gln	Asp	Ala	Lys	Gln	Ala	Glu	Ala	Val	Thr	Xaa	Pro
													20	25	30

Arg	Phe	Ile	Gly	Arg	Arg	Gln	Ser	Leu	Ile	Glu	Asp	Ala	Arg	Lys	Glu
													35	40	45

Arg	Glu	Ala	Val	Ala	Ser	Ser	Glu									
												50	55	60		

Pro	Gly	Asn	Pro	Leu	Glu	Ala	Val	Val	Phe	Glu	Glu	Arg	Asp	Gly	Asn	
												65	70	75	80	

Ala	Val	Leu	Asn	Leu	Leu	Phe	Ser	Leu	Arg	Gly	Thr	Lys	Pro	Ser	Ser	
												85	90	95		

Leu	Ser	Arg	Ala	Val	Lys	Val	Phe	Glu	Thr	Phe	Glu	Ala	Lys	Ile	His	
												100	105	110		

His	Leu	Glu	Thr	Arg	Pro	Ala	Gln	Arg	Pro	Leu	Ala	Gly	Ser	Pro	His	
												115	120	125		

Leu	Glu	Tyr	Phe	Val	Arg	Phe	Glu	Val	Pro	Ser	Gly	Asp	Leu	Ala	Ala	
												130	135	140		

Leu	Leu	Ser	Ser	Val	Arg	Arg	Val	Ser	Asp	Asp	Val	Arg	Ser	Ala	Arg	
												145	150	155	160	

Glu	Asp	Lys	Val	Pro	Trp	Phe	Pro	Arg	Lys	Val	Ser	Glu	Leu	Asp	Lys	
												165	170	175		

Cys	His	His	Leu	Val	Thr	Lys	Phe	Asp	Pro	Asp	Leu	Asp	Leu	Asp	His	
												180	185	190		

Pro	Gly	Phe	Ser	Asp	Gln	Val	Tyr	Arg	Gln	Arg	Arg	Lys	Leu	Ile	Ala	
												195	200	205		

Glu	Ile	Ala	Phe	Gln	Tyr	Lys	His	Gly	Glu	Pro	Ile	Pro	His	Val	Glu	
												210	215	220		

Tyr	Thr	Ala	Glu	Ile	Ala	Thr	Trp	Lys	Glu	Val	Tyr	Val	Thr	Leu		
												225	230	235	240	

Lys	Gly	Leu	Tyr	Ala	Thr	His	Ala	Cys	Arg	Glu	His	Leu	Glu	Gly	Phe	
												245	250	255		

Gln	Leu	Leu	Glu	Arg	Tyr	Cys	Gly	Tyr	Arg	Glu	Asp	Ser	Ile	Pro	Gln	
												260	265	270		

Leu	Glu	Asp	Val	Ser	Arg	Phe	Leu	Lys	Glu	Arg	Thr	Gly	Phe	Gln	Leu	
												275	280	285		

Arg	Pro	Val	Ala	Gly	Leu	Leu	Ser	Ala	Arg	Asp	Phe	Leu	Ala	Ser	Leu	
												290	295	300		

Ala	Phe	Arg	Val	Phe	Gln	Cys	Thr	Gln	Tyr	Ile	Arg	His	Ala	Ser	Ser	
												305	310	315	320	

Pro	Met	His	Ser	Pro	Glu	Pro	Asp	Cys	Cys	His	Glu	Leu	Leu	Gly	His	
												325	330	335		

Val	Pro	Met	Leu	Ala	Asp	Arg	Thr	Phe	Ala	Gln	Phe	Ser	Gln	Asp	Ile	
												340	345	350		

Gly	Leu	Ala	Ser	Leu	Gly	Ala	Ser	Asp	Glu	Glu	Ile	Glu	Lys	Leu	Ser	
												355	360	365		

Thr	Val	Tyr	Trp	Phe	Thr	Val	Glu	Phe	Gly	Leu	Cys	Lys	Gln	Asn	Gly	
												370	375	380		

Glu Leu Lys Ala Tyr Gly Ala Gly Leu Leu Ser Ser Tyr Gly Glu Leu

-continued

385	390	395	400
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Leu His Ser Leu Ser Glu Glu Pro Glu Val Arg Ala Phe Asp Pro Asp			
405	410	415	

Thr Ala Ala Val Gln Pro Tyr Gln Asp Gln Thr Tyr Gln Pro Val Tyr			
420	425	430	

Phe Val Ser Glu Ser Phe Asn Asp Ala Lys Asp Lys Leu Arg Asn Tyr			
435	440	445	

Ala Ser Arg Ile Gln Arg Pro Phe Ser Val Lys Phe Asp Pro Tyr Thr			
450	455	460	

Leu Ala Ile Asp Val Leu Asp Ser Pro His Thr Ile Gln Arg Ser Leu			
465	470	475	480

Glu Gly Val Gln Asp Glu Leu His Thr Leu Ala His Ala Leu Ser Ala			
485	490	495	

Ile Ser

```

<210> SEQ ID NO 28
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 28

```

Thr Gly Pro Leu Xaa Pro Gly Pro Phe			
1	5		

```

<210> SEQ ID NO 29
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 29

```

Tyr Ser Pro Thr Xaa Pro Thr Tyr Ser Pro Thr Xaa Pro Lys Lys Lys			
1	5	10	15

```

<210> SEQ ID NO 30
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 30

```

Ala Pro Arg Xaa Pro Gly Gly Arg Arg			
1	5		

<210> SEQ ID NO 31

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```

<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 31

```

Arg Arg Pro Arg Xaa Pro Ala Lys Leu Ser Phe Phe Phe Pro Ser
 1 5 10 15

```

<210> SEQ ID NO 32
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 32

```

Pro Pro Leu Met Xaa Pro Pro Phe Tyr
 1 5

```

<210> SEQ ID NO 33
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 33

```

Lys Gln Ala Glu Ala Val Thr Xaa Pro Arg
 1 5 10

```

<210> SEQ ID NO 34
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 34

```

Lys Asn Ile Val Thr Pro Arg Xaa Pro Pro Pro Ser Gln Gly Lys
 1 5 10 15

```

<210> SEQ ID NO 35
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 35

```

-continued

Thr Leu Ser Pro Ile Ala Pro Arg Xaa Pro Ala Lys Leu Ser Phe Gln
 1 5 10 15

Phe Pro Ser Ser
 20

<210> SEQ ID NO 36
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 36

Lys Arg Glu Leu Val Glu Pro Leu Xaa Pro Ser Gly Glu Ala Pro Asn
 1 5 10 15

Gln Ala Leu Leu Arg
 20

<210> SEQ ID NO 37
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 37

Tyr Ser Pro Thr Xaa Pro Thr Tyr Ser Pro Thr Xaa Pro Lys Lys Lys
 1 5 10 15

<210> SEQ ID NO 38
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 38

Glu Glu Glu Asp Gly Thr Gly Xaa Pro Gln Leu Asn Asn Arg
 1 5 10

<210> SEQ ID NO 39
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (14)..(14)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 39

-continued

Met	Lys	Asp	Asp	Lys	Glu	Glu	Glu	Asp	Thr	Gly	Xaa	Pro	Gln
1				5			10				15		

Leu	Asn	Asn	Arg
		20	

```

<210> SEQ ID NO 40
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 40

```

Phe	Asn	Glu	Leu	Ala	Xaa	Pro	Phe	Glu	Asn	Glu
1				5			10			

```

<210> SEQ ID NO 41
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 41

```

Glu	Val	Gly	Leu	Phe	Asn	Glu	Leu	Ala	Xaa	Pro	Phe	Glu	Asn	Glu	Phe
1				5			10				15				

Lys Lys Ala

```

<210> SEQ ID NO 42
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 42

```

Val	Asp	Lys	Val	Thr	Xaa	Pro	Thr	Lys	Val
1				5			10		

```

<210> SEQ ID NO 43
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 43

```

Leu	Trp	Glu	Lys	Gln	Ser	Val	Asp	Lys	Val	Thr	Xaa	Pro	Thr	Lys	Val
1				5			10			15					

```

<210> SEQ ID NO 44
<211> LENGTH: 11

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 44

Leu Tyr Arg Ser Pro Xaa Met Pro Glu Asn Leu
1 5 10

<210> SEQ ID NO 45
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 45

Arg Ser Gly Leu Tyr Arg Ser Pro Xaa Met Pro Glu Asn Leu Asn Arg
1 5 10 15

Pro Arg Leu

<210> SEQ ID NO 46
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 46

Pro Gly Pro Gly Xaa Pro Val Pro Thr Gly
1 5 10

<210> SEQ ID NO 47
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 47

Ser Thr Pro Gly Pro Gly Xaa Pro Val Pro Thr Gly Ser Val
1 5 10

<210> SEQ ID NO 48
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

-continued

<400> SEQUENCE: 48

Asp	Leu	Glu	Leu	Pro	Leu	Xaa	Pro	Ser	Leu	Leu	Gly
1				5					10		

<210> SEQ_ID NO 49
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 49

Arg	Asp	Leu	Glu	Leu	Pro	Leu	Xaa	Pro	Ser	Leu	Leu	Gly	Gly	Pro	Gly
1					5				10			15			

Pro Glu

<210> SEQ_ID NO 50
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 50

Gly	Pro	Gly	Pro	Glu	Arg	Xaa	Pro	Gly	Ser	Gly	Ser	Gly
1				5				10				

<210> SEQ_ID NO 51
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 51

Leu	Gly	Gly	Pro	Gly	Pro	Glu	Arg	Xaa	Pro	Gly	Ser	Gly	Ser	Gly	Ser
1					5				10			15			

Gly Leu Gln Ala
20

<210> SEQ_ID NO 52
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 52

-continued

Ser Thr Leu Xaa Pro Ile Ala Pro Arg Xaa Pro Ala Lys
 1 5 10

```
<210> SEQ ID NO 53
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (13)..(13)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 53
```

His Phe Trp Ser Thr Leu Xaa Pro Ile Ala Pro Arg Xaa Pro Ala Lys
 1 5 10 15

Leu Ser Phe

```
<210> SEQ ID NO 54
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 54
```

Pro Val Val Leu Xaa Pro Gly Pro Gln Lys Pro
 1 5 10

```
<210> SEQ ID NO 55
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 55
```

Gly Leu Ser Thr Pro Val Val Leu Xaa Pro Gly Pro Gln Lys
 1 5 10

```
<210> SEQ ID NO 56
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 56
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Tyr Leu Ala Leu Asp Phe Gln Pro Ser Xaa Pro Ser Pro His Arg Lys
 1 5 10 15

<210> SEQ ID NO 57

-continued

```

<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 57

```

Val Asp Tyr Leu Ala Leu Asp Phe Gln Pro Ser Xaa Pro Ser Pro His
1 5 10 15

Arg Lys Pro

```

<210> SEQ ID NO 58
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 58

```

Met Thr Ile Leu Gln Ala Pro Xaa Pro Ala Pro Ser Thr Ile
1 5 10

```

<210> SEQ ID NO 59
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 59

```

Thr Ile Leu Gln Ala Pro Xaa Pro Ala Pro Ser Thr Ile Pro Gly
1 5 10 15

```

<210> SEQ ID NO 60
<211> LENGTH: 24
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (19)..(19)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 60

```

Ile Ser Ile Pro Xaa Pro Pro Val Thr Xaa Pro Glu Gly Asp Asp Arg
1 5 10 15

Pro Glu Xaa Pro Glu Tyr Ser Gly
20

-continued

```

<210> SEQ ID NO 61
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 61

```

Glu Gly Asp Asp Arg Pro Glu Xaa Pro Glu Tyr Ser Gly Gly Asn Ile
 1 5 10 15

```

<210> SEQ ID NO 62
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 62

```

Pro Pro Val Thr Xaa Pro Glu Gly Asp Asp Arg Pro Glu
 1 5 10

```

<210> SEQ ID NO 63
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 63

```

Ala Ile Ile Ser Ile Pro Xaa Pro Pro Val Thr
 1 5 10

```

<210> SEQ ID NO 64
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 64

```

Phe Arg Gly Phe Xaa Phe Val Ala Thr Gly
 1 5 10

```

<210> SEQ ID NO 65
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

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-continued

<400> SEQUENCE: 65

Ala His Gln Leu Phe Arg Gly Phe Xaa Phe Val Ala Thr Gly Leu Met
 1 5 10 15

Glu Asp

<210> SEQ ID NO 66

<211> LENGTH: 18

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (8)..(8)

<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 66

Tyr Ala His Gln Gln Pro Pro Xaa Pro Leu Pro Val Tyr Ser Ser Ser
 1 5 10 15

Ala Lys

<210> SEQ ID NO 67

<211> LENGTH: 13

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (7)..(7)

<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 67

Ala His Gln Gln Pro Pro Xaa Pro Leu Pro Val Tyr Ser
 1 5 10

<210> SEQ ID NO 68

<211> LENGTH: 14

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (6)..(6)

<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 68

Lys Ser Glu Pro Ser Xaa Pro Asp His Gly Ser Ser Ala Ile
 1 5 10

<210> SEQ ID NO 69

<211> LENGTH: 12

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (5)..(5)

<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 69

Ser Glu Pro Ser Xaa Pro Asp His Gly Ser Ser Ala
 1 5 10

-continued

<210> SEQ ID NO 70
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 70

Arg Gly Ala Arg Ala Xaa Pro Ala Thr Gln Pro
1 5 10

<210> SEQ ID NO 71
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 71

Leu Pro Pro Ser Ala Xaa Gly Pro Asp Ala Thr Val Gly
1 5 10

<210> SEQ ID NO 72
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 72

Val Gly Gly Pro Ala Pro Xaa Pro Leu Leu Pro Pro Ser Ala
1 5 10

<210> SEQ ID NO 73
<211> LENGTH: 40
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (21)..(21)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (33)..(33)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 73

Arg Gly Gly Ala Arg Ala Xaa Pro Ala Thr Gln Pro Pro Pro Leu Leu
1 5 10 15

Pro Pro Ser Ala Xaa Gly Pro Asp Ala Thr Val Gly Gly Pro Ala Pro
20 25 30

Xaa Pro Leu Leu Pro Pro Ser Ala

-continued

35

40

```

<210> SEQ ID NO 74
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 74

```

Asn	Thr	Ile	Asp	Leu	Pro	Met	Xaa	Pro	Arg	Thr	Leu	Asp	Ser
1				5							10		

```

<210> SEQ ID NO 75
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 75

```

Ile	Asp	Leu	Pro	Met	Xaa	Pro	Arg	Thr	Leu	Asp	
1				5					10		

```

<210> SEQ ID NO 76
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 76

```

Phe	Pro	Ala	Pro	Gln	Xaa	Pro	Gly	Arg	Leu	Gln	
1				5					10		

```

<210> SEQ ID NO 77
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 77

```

Lys	Pro	Phe	Pro	Ala	Pro	Gln	Xaa	Pro	Gly	Arg	Leu	Gln	Pro	Ala	Pro
1					5				10			15			

```

<210> SEQ ID NO 78
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature

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-continued

<222> LOCATION: (6)..(6)
 <223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 78

Ser Asn Arg Pro Phe Xaa Pro Pro Thr Ser Thr Gly
 1 5 10

<210> SEQ ID NO 79
 <211> LENGTH: 18
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
 <220> FEATURE:
 <221> NAME/KEY: misc_feature
 <222> LOCATION: (9)..(9)
 <223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 79

His Ser Ser Ser Asn Arg Pro Phe Xaa Pro Pro Thr Ser Thr Gly Gly
 1 5 10 15

Ser Lys

<210> SEQ ID NO 80
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
 <220> FEATURE:
 <221> NAME/KEY: misc_feature
 <222> LOCATION: (6)..(6)
 <223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 80

Lys Ser Pro Ala Tyr Xaa Pro Gln Asn Leu Asp
 1 5 10

<210> SEQ ID NO 81
 <211> LENGTH: 15
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
 <220> FEATURE:
 <221> NAME/KEY: misc_feature
 <222> LOCATION: (8)..(8)
 <223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 81

His Ser Lys Ser Pro Ala Tyr Xaa Pro Gln Asn Leu Asp Ser Glu
 1 5 10 15

<210> SEQ ID NO 82
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
 <220> FEATURE:
 <221> NAME/KEY: misc_feature
 <222> LOCATION: (6)..(6)
 <223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 82

Val Ser Asp Ile Leu Xaa Pro Leu Glu Glu Ser
 1 5 10

-continued

<210> SEQ ID NO 83
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 83

Phe Ser Val Ser Asp Ile Leu Xaa Pro Leu Glu Glu Ser Tyr Lys							
1	5	10	15				

<210> SEQ ID NO 84
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 84

Gly Ser Ala Gly Gln Xaa Pro Asp Leu Ala His							
1	5	10					

<210> SEQ ID NO 85
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 85

Ala His His Ala Ala Xaa Pro Ala Gly Leu Gln Gly							
1	5	10					

<210> SEQ ID NO 86
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (15)..(15)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 86

Gly Ser Ala Gly Gln Xaa Pro Asp Leu Ala His His Ala Ala Xaa Pro							
1	5	10	15				

Ala Gly Leu Gln							
20							

<210> SEQ ID NO 87
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 87

Lys Gln Ala Glu Ala Val Thr Xaa Pro Arg
1 5 10

<210> SEQ ID NO 88
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 88

Lys Gln Ala Glu Ala Val Thr Xaa Pro Arg Phe Ile Gly Arg
1 5 10

<210> SEQ ID NO 89
<211> LENGTH: 24
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (19)..(19)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 89

Ile Ser Ile Pro Xaa Pro Pro Val Thr Xaa Pro Glu Gly Asp Asp Arg
1 5 10 15

Pro Glu Xaa Pro Glu Tyr Ser Cys
20

<210> SEQ ID NO 90
<211> LENGTH: 34
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic kinase active site blocker peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 90

Thr Ile Leu Gln Ala Pro Xaa Pro Ala Pro Ser Thr Asn Pro Ala Cys
1 5 10 15

Thr Ile Val Ala Thr Ile Asn Ser Ile Thr Glu Asx Leu Cys Lys Glu
20 25 30

Arg Ser

-continued

<210> SEQ ID NO 91
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide inhibitors

<400> SEQUENCE: 91

Met Pro Lys Lys Lys Pro Thr Pro Ile Gln Leu Asn Pro
1 5 10

<210> SEQ ID NO 92
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide inhibitors

<400> SEQUENCE: 92

Phe Gln Arg Lys Thr Leu Gln Arg Arg Asn Leu Lys Gly Leu Asn Leu
1 5 10 15

Asn Leu His Pro Asp
20

<210> SEQ ID NO 93
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide inhibitors

<400> SEQUENCE: 93

Met Pro Lys Lys Pro Thr Pro Ile Gln Leu Asn Pro Ala Pro Asp
1 5 10 15

Gly

<210> SEQ ID NO 94
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide inhibitors

<400> SEQUENCE: 94

Met Leu Ala Arg Arg Lys Pro Val Leu Pro Ala Leu Thr Ile Asn Pro
1 5 10 15

Thr Ile Ala Glu
20

<210> SEQ ID NO 95
<211> LENGTH: 30
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide inhibitors

<400> SEQUENCE: 95

Arg Gln Ile Lys Ile Trp Phe Gln Asn Arg Arg Met Lys Trp Lys Lys
1 5 10 15

Gly Met Pro Lys Lys Lys Pro Thr Pro Ile Gln Leu Asn Pro
20 25 30

<210> SEQ ID NO 96
<211> LENGTH: 43

-continued

<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide inhibitors

<400> SEQUENCE: 96

Gly	Tyr	Gly	Arg	Lys	Lys	Arg	Arg	Gln	Arg	Arg	Gly	Met	Pro	Lys	
1														15	
Lys	Lys	Pro	Thr	Pro	Ile	Gln	Leu	Asn	Pro	Asp	Cys	Lys	Ile	Asn	Gly
					20								30		
Ser	Ile	Thr	Glu	Asx	Leu	Cys	Lys	Glu	Arg	Ser					
					35					40					

<210> SEQ ID NO 97
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide inhibitors

<400> SEQUENCE: 97

Lys	Gly	Arg	Lys	Pro	Arg	Asp	Leu	Glu	Leu	Pro
1										10

<210> SEQ ID NO 98
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide inhibitors

<400> SEQUENCE: 98

Pro	Gln	Lys	Gly	Arg	Lys	Pro	Arg	Asp	Leu	Glu	Leu	Pro	Leu
1												10	

<210> SEQ ID NO 99
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide inhibitors

<400> SEQUENCE: 99

Ile	Asn	Val	Ala	Ile	Pro	Gly	Ile	Met	Leu	Arg	Arg	Leu	Gln	Lys	Gly
1														15	

Asn	Leu	Pro	Val	Arg
			20	

<210> SEQ ID NO 100
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide inhibitors

<400> SEQUENCE: 100

Leu	Lys	Pro	Ile	Glu	Ser	Ser	Ile	Leu	Ala	Gln	Arg	Arg	Val	Arg	Lys
1														15	

Leu	Pro	Ser	Thr
			20

<210> SEQ ID NO 101
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide inhibitors
 <400> SEQUENCE: 101

```
Leu Ser Pro Pro Ser Gln Ser Lys Leu Ala Gln Arg Arg Gln Arg Ala
1           5          10          15

Ser Leu Ser Ala Thr
20
```

<210> SEQ ID NO 102
 <211> LENGTH: 15
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide inhibitors

<400> SEQUENCE: 102

```
Arg Arg Pro Arg Ser Pro Ala Lys Leu Ser Phe Gln Phe Ala Ser
1           5          10          15
```

<210> SEQ ID NO 103
 <211> LENGTH: 15
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide inhibitors

<400> SEQUENCE: 103

```
Arg Arg Pro Arg Ser Pro Ala Lys Leu Ser Phe Phe Phe Pro Ser
1           5          10          15
```

<210> SEQ ID NO 104
 <211> LENGTH: 20
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide inhibitors

<400> SEQUENCE: 104

```
Thr Leu Ser Pro Ile Ala Pro Arg Ser Pro Ala Lys Leu Ser Phe Gln
1           5          10          15

Phe Pro Ser Ser
20
```

<210> SEQ ID NO 105
 <211> LENGTH: 14
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide inhibitors

<400> SEQUENCE: 105

```
Thr Pro Ala Thr Pro Thr Ser Gln Phe Val Phe Ser Phe Pro
1           5          10
```

<210> SEQ ID NO 106
 <211> LENGTH: 15
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Synthetic polypeptide inhibitors

<400> SEQUENCE: 106

```
Ser Pro Ala Arg Leu Gln Gly Ala Asn Thr Leu Phe Gln Phe Pro
1           5          10          15
```

-continued

<210> SEQ ID NO 107
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide inhibitors

<400> SEQUENCE: 107

Thr Pro Thr Ala Ala His Ser Gly Ser His Leu Phe Gly Phe Pro
1 5 10 15

<210> SEQ ID NO 108
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic polypeptide inhibitors

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Arg Arg Pro Arg Ser Pro Ala Lys Leu Ser Phe Ala Phe Pro Ser
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<210> SEQ ID NO 109
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<213> ORGANISM: Artificial
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Ala Ala Ala Ala
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<210> SEQ ID NO 110
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Gly Ala Gly Ala
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<210> SEQ ID NO 111
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Gly Gly Gly Gly
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<210> SEQ ID NO 112
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Ala Gly Ala Gly
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<223> OTHER INFORMATION: Synthetic peptide

<400> SEQUENCE: 114

Ala Ala Gly Gly
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<210> SEQ ID NO 115
<211> LENGTH: 4
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Gly Gly Ala Ala
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What is claimed is:

1. An isolated polynucleotide comprising a nucleotide sequence encoding a polypeptide polyligand comprising a first amino acid sequence selected from the group consisting of SEQ ID NOS: 28, 32, 36, 48, and 49 and one or more additional amino acid sequences that are at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 28, 32, 36, 48, 49, 91, 93-96 and 102, wherein Xaa of SEQ ID NOS: 28, 32, 36, 48, and 49 is any naturally occurring amino acid other than serine or threonine, and

wherein the polypeptide polyligand inhibits the kinase activity of extracellular-signal-regulated kinase (ERK).

2. The isolated polynucleotide of claim 1, wherein said polypeptide polyligand is a heteropolyligand.

3. The isolated polynucleotide of claim 1, wherein said polypeptide polyligand is linked to one or more of a localization signal, an epitope tag, or a reporter.

4. A vector comprising the isolated polynucleotide of claim 1.

5. An isolated host cell comprising the vector of claim 4.

6. The isolated polynucleotide of claim 1, operably linked to a promoter.

7. The isolated polynucleotide of claim 6, wherein said promoter is an inducible promoter.

8. The isolated polynucleotide of claim 1, wherein said one or more additional amino acid sequences are at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 28, 32, 36, 48, 49, 91, 93-96 and 102.

9. The isolated polynucleotide of claim 1, wherein said one or more additional amino acid sequences are at least 96%

35 identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 28, 32, 36, 48, 49, 91, 93-96 and 102.

10. The isolated polynucleotide of claim 1, wherein said one or more additional amino acid sequences are at least 97% 40 identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 28, 32, 36, 48, 49, 91, 93-96 and 102.

11. The isolated polynucleotide of claim 1, wherein said one or more additional amino acid sequences are at least 98% 45 identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 28, 32, 36, 48, 49, 91, 93-96 and 102.

12. The isolated polynucleotide of claim 1 wherein said one or more additional amino acid sequences are at least 99% 50 identical to an amino acid sequence selected from the group consisting of SEQ ID NOS: 28, 32, 36, 48, 49, 91, 93-96 and 102.

13. The isolated polynucleotide of claim 1, wherein said one or more additional amino acid sequences are selected 55 from the group consisting of SEQ ID NOS: 28, 32, 36, 48, 49, 91, 93-96 and 102.

14. A method of inhibiting ERK in a cell, said method comprising

(a) transfecting the vector of claim 4 into an isolated host cell that expresses ERK, and

(b) culturing the transfected host cell under conditions suitable to produce at least one copy of the polypeptide polyligand, thereby inhibiting ERK in the host cell.

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